Management of Tumour Lysis Syndrome – Joint Clinical Guidelines

Ref:CG-HAEM/2024/004

Purpose of the Guideline

The aims of this guideline are to try and predict which patients are at risk of tumour lysis syndrome and so ensure that when this complication of treatment does occur it is managed in a timely and efficient manner to ensure the optimal outcome for the patient.

Introduction

Tumour Lysis Syndrome (TLS) is a life-threatening complication that arises when the rapid lysis of tumour cells leads to the release of excessive quantities of cellular contents into the systemic circulation resulting in a metabolic disturbance characterised by:-

- Hyperkalaemia
- Hyperphosphataemia
- Hyperuricaemia
- Hypocalcaemia

This metabolic derangement may lead to acute oliguric renal failure and cardiac arrhythmias.

TLS can occur spontaneously in tumours with a very high proliferative rate, as well as following initiation of treatment. It can be classified as laboratory TLS (with no clinical manifestations) or clinical TLS (patients with life-threatening clinical abnormalities).

Diagnosis of Tumour Lysis Syndrome

TLS may be classified according to clinical or laboratory features.

Laboratory Screen for TLS

This needs to include: Urea, Creatinine, Uric acid / Urate*, Phosphate, Potassium, Albumin corrected Calcium.

***Samples for urate from patients who have received rasburicase within the last 24 hours require special handling - collect into pre-chilled lithium heparin tubes, deliver to lab by hand with sample on ice, lab must separate at 4°C and analyse within four hours. Failure to adhere to this protocol will lead to underestimation of urate due to ex-vivo conversion to allantoin.**

Cairo-Bishop definition of laboratory TLS

Laboratory TLS is considered present if levels of 2 or more serum values of the following are abnormal at presentation (as specified below) or if they change by 25% within 3 days before until 7 days after cytotoxic therapy:

- Urate / Uric acid* - >ULN or 25% increase from baseline
- Potassium - >6.0 mmol/l or 25% increase from baseline
- Phosphate - >1.45 mmol/l or 25% increase from baseline
- Albumin corrected Calcium - <1.75 mmol/l or 25% decrease from baseline

*__Not included if rasburicase has been administered within previous 24 hours.__

Cairo-Bishop definition of clinical TLS

Laboratory evidence of TLS plus 1 or more of:

- Cr > 1.5 x ULN
- Cardiac arrhythmia / sudden death
- Seizure

Prevention of Tumour Lysis Syndrome

Since TLS can develop rapidly and is difficult to treat once established, prevention is of prime importance. The identification of patients at risk for the development of TLS is the most important aspect of management, so that prophylactic measures may be initiated prior to initiation of therapy.

The table on the following page provides a summary of risk stratification and preventative management - see below table for more details:

Risk Group	Disease Type	Preventative Strategies
High	High Grade Malignancy • Burkitt's NHL • Lymphoblastic Lymphoma • ALL with WCC >100 • AML with WCC >50	• IV fluids 24 hours prior to chemotherapy- 3L/m^2/day (no K+ supplementation) • Aim for urine output >100ml/m^2/hour • Rasburicase (iv)- 7.5mg in 50ml of N saline over 30mins. • Consider split dosing chemotherapy/deferring day 1 rituximab
Intermediate - High	• High grade lymphoma with high tumour burden (High LDH (>2x ULN) or mass >10cm.	• IV fluids- 3L/m^2/day to achieve urine output >100ml/m2/hour • Rasburicase (iv)- 3mg in 50ml of N saline over 30mins. • If additional risk factors* consider increased dose rasburicase.
Intermediate - Low	• High grade lymphoma with no high risk features.	• Oral intake > 3L/day • Allopurinol
Low	• Low grade malignancy (Chronic phase CML, CLL. Low grade lymphoma, Myeloma)	• Aim for oral intake of 3L/day • Allopurinol

***Additional risk factors- Renal impairment, oliguria, disease affecting renal tract**

High risk / Intermediate-High risk patients

- Patients considered at high risk of TLS should be admitted for their first course of chemotherapy
- **Consider split dosing chemotherapy/ deferring day 1 rituximab if having R-CHOP (discuss with Consultant).**
- As soon as a "high risk" diagnosis is suspected, a TLS screen should be undertaken.
- Unless there is oliguria or acute renal dysfunction, initially hydrate at 3L/m^2/day with intravenous fluids. Consider cardiac function and risk of fluid overload.
- Diuretics (furosemide, mannitol) may be required to maintain urine output > 100ml/ m^2/hour **(contact doctor if urine output below 100ml/m^2/hour).**
- Rasburicase for prophylaxis of TLS should be initiated before administration of Day 1 of chemotherapy. **(NB Rasburicase should be given first thing on the morning of planned chemotherapy)**. Rasburicase is a recombinant form of urate oxidase, an enzyme present in most living organisms but not humans. This catalyzes the oxidation of uric acid to allantoin. Allantoin is at least 5 times more soluble than uric acid and is readily excreted by the kidneys. Allopurinol blocks the conversion of xanthines to uric acid, so this will reduce the effect of rasburicase. Therefore do **not** give allopurinol and rasburicase together.
- Rasburicase administration: Dose as per risk score in 50ml Sodium Chloride 0.9% IV infusion over 30 minutes.
- Monitor tumour lysis bloods as per proforma with additional rasburicase dosing as indicated
- No dose adjustment required for renal or hepatic impairment.
- The most common side effect is allergic reactions, mainly rash and urticaria.
- Contra-indicated in patients with G6PD deficiency.
- Consult Rasburicase SPC for full details before using.

- Allopurinol may be used if required **only after** completing rasburicase therapy.
- If possible, consideration should be given to delaying initiation of chemotherapy for 24 – 48 hours whilst supportive measures are initiated. **Once chemotherapy has commenced, a TLS screen should be undertaken at + 4 hours, then timing as guided by results and proforma, and at least once daily thereafter for 3 – 5 days. Samples should be sent urgently to the laboratory. If there is evidence of tumour lysis, samples should be sent more frequently (see section on treatment of established TLS). It is the responsibility of the ward based doctor to chase the results up in a timely fashion, and to discuss with the Haematologist on-call.**

Intermediate-Low risk patients

- Allopurinol should ideally be commenced at least 24 hours prior to chemotherapy.

(N.B. Rasburicase may be considered for patients with severe hypersensitivity to allopurinol.)

- Continue high fluid intake (>3L/day) for at least 48 hours after starting chemotherapy.

Low risk patients

- Commence allopurinol prior to chemotherapy.

Treatment of Established TLS

Any patient with evidence of TLS should be discussed immediately with the SpR or consultant on call for haematology.

General measures for treatment of laboratory TLS with or without clinical TLS include:

- Vigorous hydration to maintain urine output > 100ml/ m^2/hour
- Correction of high potassium (according to local guidelines)
- Use of rasburicase 0.2mg/kg IV
- Allopurinol should be stopped when rasburicase is commenced.
- Seek ICU / renal specialist advice as haemofiltration / dialysis may be required.
- Correction of low calcium should be avoided when there is concurrent high phosphate because of the risk of precipitation of insoluble calcium phosphate. Only symptomatic hypocalcaemia should be corrected.
- Moderate / asymptomatic hyperphosphataemia may be initially treated by maintaining adequate hydration and use of an oral phosphate binder eg Aludrox. However, a renal specialist should be notified regarding the patient in case dialysis is required.
- Alkalinisation of urine is not recommended when using rasburicase – although uric acid is 15 times more soluble at pH 7 than at pH 5, uric acid levels will be rapidly reduced when rasburicase is used. In contrast, phosphate is more soluble in acid medium and so there is an increased risk of calcium phosphate precipitation in the kidney if urine is alkalinised.
- However, alkalinisation may be considered if rasburicase is not available and the patient is severely acidotic.

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References:

Coiffier, B et al; JCO 2008; 26 (16): 2767 - 2777

Cairo et al; Br J Haem (2004); 127: 3 – 11

BCSH guidelines for management of tumour lysis syndrome: Br J Haem; 169; Pg 661-671

Triffilio et al; Bone marrow transplanatation; 46; Pg 800-805

Coutsouvelis et al; Br J of clinical pharmacology; 75:2; Pg 550-553

Fasturtec, Summary of Product Characteristics, Sanofi-Aventis