Prevention and Management of Tumour Lysis Syndrome

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Contents

The National Strategic Clinical Network for Cancer (Cancer Network) is part of the NHS Wales Executive, working to improve outcomes and care for cancer patients in Wales.
Under the non-Surgical Oncology Work stream (comprising Systemic Anti-Cancer Therapy, Acute Oncology, Genomics and Cancer Outcome and Services Dataset (COSD)), the Cancer Network works to develop areas of best practice and align priorities and processes in SACT delivery across Wales.

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0.1	Nov 2019	Anthony Cadogan		Minor additions to Febuxostat warnings following MHRA update
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Scope

This document is for healthcare professionals delivering systemic anti cancer therapy (SACT) for Adult patients with malignant disease in in-patient and outpatient settings within Cancer and Clinical Haematology services.

Background

Tumour lysis syndrome (TLS) is a potentially life-threatening metabolic syndrome caused by the breakdown of malignant cells.

It is characterised by hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia with potentially severe consequences such as acute kidney injury, cardiac arrhythmias, seizures and death.

While most cases of TLS are observed in the setting of chemotherapy induction, some patients might experience spontaneous TLS prior to starting treatment e.g. acute leukaemia with very high white cell count.

TLS can be classified as Laboratory TLS (with no clinical manifestation) or Clinical TLS - see 1.6 below. Clinical TLS is associated with a high mortality, therefore prevention is the key strategy.

TLS risk in patients with haematological malignancies is primarily dependent upon the pathological diagnosis. Patients can be risk stratified according to diagnosis and managed accordingly.

1.1. Cairo-Bishop Criteria (2004):

Laboratory TLS: Two or more of the following abnormalities:
1. Uric acid ≥ Upper limit of normal (ULN) or 25% increase from baseline 2. Potassium ≥ULN or 25% increase from baseline 3. Phosphate ≥ ULN or 25% increase from baseline 4. Calcium ≤ Lower limit of normal (LLN) or 25% decrease from baseline

Clinical TLS: A patient with laboratory TLS and at least one of following:
1. Creatinine ≥ 1.5x ULN 2. Cardiac arrhythmia 3. Seizure 4. Sudden death

Screening Investigations for TL

The TLS screen consists of a minimum of:

Urea
Creatinine
Urate (Uric Acid) – *see 2.2 below*
Potassium
Albumin
Corrected Calcium
Phosphate

If rasburicase has been administered within 24 hours of blood sampling, *in vitro* degradation of urate will continue, possibly resulting in falsely low urate levels. The availability of measures to minimise this effect must be considered when planning local TLS policies.

Pharmacological interventions for the prophylaxis and management of TLS

Allopurinol

An oral xanthine oxidase inhibitor. The usual oral dose is 300mg daily (but see below under intermediate risk). The dose should be reduced in renal impairment. If CrCl <20mL/min, usually to a maximum of 100-200mg.

Available as 100mg and 300mg tablets in packs of 28.

Febuxostat (Adenuric®)

An oral xanthine oxidase inhibitor. The recommended oral dose of Febuxostat is 120 mg once daily. It is indicated in patients who are considered intermediate or high risk of TLS. It should be started two days before starting chemotherapy and continued for 7 to 9 days.

Febuxostat is not recommended for patients with history of major cardiovascular disease for example, myocardial infarction, stroke, or unstable angina (MHRA, 2019).

Available as 120mg and 80mg tablets in packs of 28.

Interaction with Mercaptopurine

Both allopurinol and febuxostat are expected to increase the risk of haematological toxicity when given with mercaptopurine. Concomitant use must be avoided.

Rasburicase

A recombinant urate oxidase given by intravenous infusion. Rasburicase should be given 30-60 minutes prior to treatment. The total dose should be diluted in 50mL of Sodium Chloride 0.9% and administered over 30 minutes. No dose adjustments of renal or hepatic impairment are required.

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.

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 (BCSH, 2015).

The full licenced dose of rasburicase of 200micrograms/kg daily for up to 7 days may be required in those patients at very high risk of TLS. The dose banding schedule in Table 1 can be used to guide dosing in this indication.

Patient weight	Dose
34 – 41kg	7.5mg
41 – 49kg	9mg
49 – 56kg	10.5mg
56 – 64kg	12mg
64 – 71kg	13.5mg
71 - 79kg	15mg
79 - 86kg	16.5mg
86 - 94kg	18mg
94 - 101kg	19.5mg
101 - 109kg	21mg

Table 1: Dose banding schedule for Rasburicase

Rasburicase is contraindicated in patients with G6PD deficiency due to the risk of inducing severe haemolysis. Patients should be screened for G6PD deficiency prior to starting treatment with rasburicase. Patients should be managed with fluids and allopurinol as for high risk patients; these patients would require careful monitoring for tumour lysis syndrome.

Pre-treatment with allopurinol is not required for patients who receive Rasburicase.

Laboratory Testing of Uric Acid Levels

Rasburicase will cause enzymatic degradation of uric acid within blood samples that are left at room temperature, resulting in a falsely low uric acid levels.

The following steps should be taken to ensure accurate measurement of plasma uric acid in patients where rasburicase has been administered:

1. Inform the lab prior to taking the sample (the lab may need to cool the centrifuge)
2. Take the blood into pre-chilled lithium heparin tubes
3. Immediately immerse the tube in ice
4. Convey the sample directly to the lab for measurement

Where these steps are not reliably available (including out of hours), it may be argued that accurate measurement of uric acid levels is not possible after the administration of rasburicase, and therefore due consideration should be given to administering the full, licenced dose (in place of the 3mg stat dose).

Prophylaxis

All patients whose diagnosis carries a risk of TLS should be risk assessed upon diagnosis and have their TLS screen checked prior to treatment (see Appendix 1). Assessment should take into account:

i. whether there is evidence of laboratory or clinical TLS at diagnosis
ii. whether the tumour itself confers high risk (see Appendix 1)
iii. other risk factors that impact on risk of TLS development, e.g.:
    a. pre-existing renal failure,
    b. advanced age,
    c. renal involvement by tumour,
    d. efficacy of proposed treatment
    e. use of predisposing concomitant medications

The assessment of TLS risk in patients receiving Venetoclax (Venclyxto®) is complex, and is described separately in Venetoclax (Venclyxto®).

Low risk Patients

Patients with low grade and low bulk disease can be managed by ensuring good hydration and monitoring electrolytes, with low threshold to adding fluids and allopurinol (usually for up to first 7 days after treatment) if needed.

Intermediate Risk Patients

For many patients, prophylaxis with allopurinol and oral hydration will be adequate. However a suitable alternative strategy is administration of a single dose of rasburicase (usually 3mg but 7.5mg has been used)

Rasburicase should be used for patients with renal impairment or who are allergic to Allopurinol

For all intermediate risk patients:

a. Monitor renal function and electrolytes (as part of regular TLS monitoring)
b. Ensure adequate hydration

High Risk Patients:

- Acute lymphoblastic or myeloid leukaemia with WBC >100×10^9/L
- Burkitt Lymphoma or Lymphoblastic Lymphoma.
- High-grade Lymphoma (diffuse large B-cell non-Hodgkin lymphoma (DLBCL) or T-cell non-Hodgkin Lymphoma) with bulky disease defined as:
    - LDH > twice the upper limit of normal
    - Tumour bulk on imaging, i.e. mass >10cm in diameter

- Bulky Germ Cell, neuroblastoma or Small-Cell Lung Cancer with renal impairment, renal involvement or electrolyte disturbance.

Patients titrating on Venetoclax – see Venetoclax (Venclyxto®)

Discuss all patients meeting the above criteria with a Consultant.

For High Risk Patients:

Ensure adequate hydration, avoiding added potassium unless specifically requested by a Consultant.

Monitor urine output, aiming for 100mL/m^2/hour where clinically appropriate. Loop diuretics may be used if hydration measures do not produce a satisfactory urine output, however these may cause precipitation of uric acid and calcium phosphate in the tubules and should therefore be avoided in patients with renal obstruction or volume depletion.

Close monitoring of U&E, phosphate, calcium and uric acid, including baseline values.

Single dose of 3mg Rasburicase, repeat dose in 24 hours if necessary. In extremely high risk patients or where facilities for testing blood samples in the presence of *in vivo* rasburicase are not available (see Laboratory Testing of Uric Acid Levels), 200microgram/kg DAILY dosing should be used. (BCSH, 2015)

Daily assessment is required, including TLS screen, blood pressure, heart rate, and respiratory rate.

Flowchart for Management of Established TLS

Management of Established Tumour Lysis Syndrome

Early recognition is vital.

Involve renal +/- intensive care teams as soon as possible

Renal dialysis is indicated in cases of intractable fluid overload, hyperkalaemia, hyperuricemia, hyperphosphatemia or hypocalcaemia.

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Start **Rasburicase** at full dose (200micrograms/kg/day, less any doses already received in the last 24 hours).

- No dose adjustments of renal or hepatic impairment are required.
- The total dose should be diluted in 50mL of Sodium Chloride 0.9% and administered over 30 minutes.
- The dose should be assessed daily, with a usual treatment duration of between 3 and 7 days

Prescribe intravenous fluid replacement to ensure urine output of 100mL/m^2/hour

Correct electrolyte disturbances as guided by local policy (except asymptomatic hypocalcaemia – see below)

Arrange at least daily TLS screen:

- U&E
- Bone Profile
- Urate

Correct hypocalcaemia only if the patient is symptomatic

Alkalinisation of the urine is not recommended.

Venetoclax (Venclyxto®)

In Chronic Lymphocytic Leukaemia (CLL)

Venetoclax presents additional challenges in the management of Tumour Lysis Syndrome. It can cause rapid reduction in tumour, and therefore poses a risk for TLS during the early dose-titration phase (usually the first 5 weeks) in all patients with Chronic Lymphocytic Leukaemia (CLL), regardless of tumour burden and other patient characteristics.

Electrolyte disturbances consistent with TLS can occur as early as 6-8 hours following the first dose of venetoclax and at each dose increase.

Prior to treatment with Venetoclax, there should be an assessment of TLS risk including radiographic tumour burden assessment and evaluation of baseline blood biochemistry (with appropriate correction) and patient comorbidities. Impaired renal function (Creatinine Clearance <80mL/min) further increases TLS risk.

Prophylaxis should be in line with TLS Risk. Local policy should be followed.

In Acute Myeloid Leukaemia (AML)

The risk and incidence of TLS in AML patients is generally lower than in CLL patients. The venetoclax daily dose titration is 3 days when used with azacitidine, or 4 days when used with low-dose cytarabine; in trials the risk of TLS was marginally higher with the cytarabine combination than with azacitidine.

Prophylaxis measures listed below should be followed:

- All patients should have white blood cell count $<25x10^9$/L prior to initiation of venetoclax. Cytoreduction prior to treatment may be required (usually this is with hydroxycarbamide, but discuss with a consultant).

- All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during the dose-titration phase.

- Assess TLS bloods, and correct pre-existing electrolyte abnormalities prior to initiation of treatment with venetoclax.

- Monitor TLS bloods at pre-dose, 6 to 8 hours after each new dose during titration, and 24 hours after reaching the final dose.

- For patients with risk factors for TLS (e.g. circulating blasts, high burden of leukaemia involvement in bone marrow, elevated LDH levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing the venetoclax starting dose.

Appendix 1: Tumour Lysis Syndrome Risk by Diagnosis

	Low Risk	Intermediate Risk	High Risk
Solid Tumours:	Majority of cases	Bulky Germ Cell, neuroblastoma or Small-Cell Lung Cancer	Intermediate risk with renal dysfunction or involvement, raised urate, potassium or Phosphate.
CLL:	Treatment with alkylating agents only	1: WBC ≥50×10^9/L *or* 2: Treatment with targeted therapies or biological agents.	
CML:	Chronic Phase		
AML:	1: WCC less than 25x10^9/L and LDH < 2 x ULN	1: LDH > 2 x ULN *or* 2: WCC >25x10^9/L and <100x10^9/L	1: WCC >100x10^9/L
ALL:		1: WCC<100x10^9/L *or* 2: LDH <2 x ULN	1: LDH >2 x ULN *or* 2: WCC>100x10^9/L
Burkitt lymphoma /leukaemia:		1: Early stage *or* 2: LDH <2 x ULN	1: Advanced stage *or* 2: LDH >2 x ULN
DLBCL and Peripheral T-NHL:	Non-bulky disease with LDH <2 x ULN	Non-bulky disease with LDH >2 x ULN	Bulky disease with LDH > 2 x ULN Renal impairment and/or electrolyte disturbance
Follicular Lymphoma:		Renal impairment and/or electrolyte disturbance	
Hodgkin's lymphoma:		Renal impairment and/or electrolyte disturbance	
Marginal Zone Lymphoma:		Renal impairment and/or electrolyte disturbance	
Mantle cell NHL:	non-Blastoid version	LDH >2 x ULN	Blastoid version with LDH >2 x ULN
Cutaneous T-Cell NHL:		Renal impairment and/or electrolyte disturbance	
MALT:		Renal impairment and/or electrolyte disturbance	
Small lymphocytic Lymphoma:		Renal impairment and/or electrolyte disturbance	
Anaplastic large cell NHL:		Renal impairment and/or electrolyte disturbance	
Multiple Myeloma:			

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