Nottingham University Hospitals NHS
NHS Trust

Tumour Lysis Syndrome Management and Prevention in Haematological Patients

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Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	Adult clinical haematology patients
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Rasburicase flat dose recommended for intermediate/ high tumour lysis risk patients
Summary of evidence base this guideline has been created from:	NUH chemotherapy guidelines and SOPS Venetoclax summary of prescribing information.
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

GUIDELINE FOR THE MANAGEMENT AND PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME IN HAEMATOLOGICAL MALIGNANCIES

Purpose of the Guideline

The aim of this guideline is to predict and prevent patients with haematological malignancies from developing serious tumour lysis syndrome (TLS) and to 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.

Definition of Tumour Lysis Syndrome

Acute tumour lysis syndrome (TLS) occurs when the rapid destruction of malignant cells releases intracellular contents which cause hyperuricaemia, hyperphosphatemia, hyperkalaemia, uraemia and / or renal failure and hypocalcaemia. These biochemical disturbances can progress to clinical features including nausea, diarrhoea, muscle weakness, tetany, arrhythmias, seizures and sudden death. It occurs in many types of haematological malignancy but is most common in tumours with a rapid proliferation rate and high sensitivity to treatment.

Cairo-Bishop criteria(REF) are used to establish diagnosis of TLS, which requires presence of > 2 of the following laboratory abnormalities:

Urate	> 476 µmol/l or 25% increase
Potassium	> 6.0 mmol/l or 25% increase
Phosphate	> 1.45 mmol/l or 25% increase
Calcium	< 1.75 mmol/l or 25% decrease
LDH	> 2x normal range
Urea / creatinine	Evidence of renal impairment

Laboratory TLS will be diagnosed in the presence of >2 abnormalities but unaltered renal function.
Clinical TLS will be diagnosed when there is biochemical TLS accompanied by renal impairment.

Pathophysiology

Uric acid is a breakdown product of purines into xanthine and then to uric acid by the enzyme xanthine oxidase. Normally the kidney excretes 500mg of uric acid per day; at physiological pH it is 99% ionised with a pKa of 5.4. When malignant cells break down rapidly, up to 10g of uric acid are passed through the kidney per day. At normal urinary pH this can result in uric acid crystals forming within and obstructing the renal tubules leading to acute renal failure.

Malignant cells contain large amounts of phosphate which is released upon cell lysis. Renal excretion becomes overloaded and may be impaired in the presence of a urate nephropathy. Hyperphosphataemia results in hypocalcaemia. Similarly lysed cells release large amounts of potassium which can result in hyperkalaemia.

Risk Factors

Treatment with Venetoclax (AML and CLL patients): See specific risk assessment/management in appendix 1.

Risk stratification based on Cairo-Bishop criteria (Cairo et al, 2010)

TLS risk factors	
High risk	• AML with WBC >100 • ALL with WBC >100, mediastinal mass or LDH >2X ULN • Burkitt's lymphoma/leukaemia advanced stage or if LDH >2 X ULN • Lymphoblastic Lymphoma • Bulky lymphoma with raised LDH • Prior uric acid or phosphate or potassium above ULN becomes high risk • Renal dysfunction or renal involvement by disease
Intermediate risk	• AML with WBC >25 but <100 or LDH >2X ULN • ALL with WBC <100 or LDH <2XULN • Non bulky lymphoma with raised LDH
Low risk	• Myeloma • CML • CLL non-venetoclax treatment, AML with WBC <25 and LDH <2X ULN • Hodgkin's, small lymphocytic, follicular, marginal zone B cell, MALT. Mantle cell, cutaneous t cell. • Lymphoma with normal LDH

Prevention of Tumour Lysis Syndrome

Low Risk Patients

- Patients considered to be at LOW RISK of tumour lysis syndrome who are having intravenous chemotherapy should be started on ALLOPURINOL prior to the start of treatment. For patients on oral chemotherapy ALLOPURINOL should be considered. They should be advised to drink plenty of fluids daily (3 litres per day) but no special monitoring is necessary

Intermediate and High Risk Patients

- Patients considered to be at INTERMEDIATE or HIGH RISK of TLS should be admitted for their first course of chemotherapy

- Baseline investigations should include U&E, Ca and PO4, urate, LDH, clotting screen including D Dimer and an ECG

- Those in the INTERMEDIATE risk category should receive ALLOPURINOL 300mg daily (provided normal renal function) 24 hours prior to the start of chemotherapy and continued for a minimum of 7 days, until risk is deemed low.

- Those in the HIGH RISK category should receive a single dose of IV RASBURICASE at a fixed dose of 3mg or 6mg in 50 ml Sodium chloride 0.9% over 30 minutes 4 hours pre chemotherapy. A dose of 0.2 mg/kg/day can be considered as an alternative following discussion with a Consultant Haematologist. Allopurinol should be stopped as it reduces the efficacy of rasburicase. Please note the use of rasburicase carries a high risk of haemolysis in individuals known to have G6PD deficiency, the decision to use rasburicase should be made by a consultant only, after weighting risks and benefits.

- Intra-venous hydration should be commenced using Normal Saline at 3 l/m^2/day to maintain a urine output of > 100 ml/m^2 /hr. Usually alternating bags of N Saline and 5% Dextrose are recommended. No additives are required (potassium, calcium or phosphate where possible)

- If hypokalaemia develops (K+ < 3.0mmol/l) then K+ supplementation can be used judiciously but stopped before commencement of chemotherapy

- If the urine output is inadequate consider 0.5 -1 mg/kg IV furosemide (at a rate not exceeding 4mg/min)

- Bloods should be repeated 2 and 6 hours after the start of chemotherapy. **(Note that following rasburicase therapy urate levels need to be sent on ice for accurate levels to be measured).** Repeat doses may be required for 3-5 days

- If no abnormality is present on the 6 hour sample repeat bloods at 18 hours.

- Please note that detectable uric acid levels (even within normal values) might be indicative of TLS in the context of rasburicase treatment, please seek senior advice for interpretation of results in these cases.

- If abnormalities are present on the 6 hour sample repeat the bloods at 2-6 hourly intervals depending on the severity and clinical situation and follow the Guideline for the Management of Established TLS (see below)

- Bloods should be repeated daily for up to 5 days since delayed onset TLS has been described

- It is the responsibility of the Haematology Specialist Trainee in charge of the patient to ensure that an adequate management plan is present in the notes for each patient and that the necessary blood samples are taken by the out of hours team. The senior nurse on the shift also needs to ensure that the samples are sent and that the results are reviewed by the medical staff

- Urinary alkalinisation is NOT usually recommended. Raising the urinary pH to 7 does increase the solubility of uric acid and prevent obstructive uropathy, however, in patients receiving allopurinol xanthine can then be precipitated in the renal tubules leading to nephropathy. Furthermore if hyperphosphataemia develops then having a pH > 7 can lead to precipitation of calcium phosphate. Alkalinisation prior to chemotherapy administration should only be commenced at specific Consultant request and MUST BE STOPPED when chemotherapy is started. Alkalinisation is best achieved by adding 50 ml of 8.4% $NaHCO_3$ to every litre of fluid replacement (i.e. 50 mmol $NaHCO_3$/l)

Management of Established Tumour Lysis Syndrome

- All patients should receive aggressive intravenous hydration as outlined above with NO urinary alkalinisation

- A urinary catheter should be passed with careful monitoring of fluid balance and urine output

- Blood monitoring of U&E, Ca, PO_4, urate should be every 2-6 hours depending on the severity as above

- Rasburicase should be given if patient has not already received it, or repeated again if a repeat sample (must be sent on ice) shows a measurable uric acid level above 250 ng/ml (maximum 5 doses). Dose will be 0.2 mg/kg.

- An ECG should be performed

- Inform the renal Specialist Trainee on call about the patient

- Inform the patient's Consultant or Consultant on call about the patient

- Consider transferring the patient to HDU for management
- Chemotherapy treatment should be discussed with a Consultant but will usually need to be suspended until the TLS has resolved
- Restart allopurinol at 48 hours if urate stable
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Hyperphosphataemia

- A level of > 1.45 mmol/l in adults is abnormal
- May lead to nausea, vomiting, diarrhoea, lethargy, fits and precipitation of calcium phosphate
- IV and oral calcium supplements should be avoided
- Levels > 2.1 mmol/l should be treated with oral chelation using a phosphate binder. Sevelamer 800mg tablets (2.4 - 4.8g/day in 3 doses) would be the first line oral chelator. Seek advice from renal if needed.
- Levels > 4 mmol/l will usually require more aggressive therapy usually with haemodialysis or haemofiltration and must be discussed urgently with the renal team

Hypocalcaemia

- If asymptomatic then this should not be treated as treatment can precipitate further calcium phosphate deposition in the kidneys. Calcium levels should correct as other abnormalities improve
- If < 1.75 mmol/l (or 25% drop from baseline) and symptomatic with severe tetany, seizures or prolonged QT interval on ECG or hyperkalaemia then give calcium gluconate 10ml 10% intravenously (risk of nephrocalcinosis)

Hyperkalaemia (Please refer to trust hyperkalemia guidelines)

- If potassium > 6mmol/l (or 25% increase from baseline) but < 7mmol/l in an asymptomatic patient, initiate ECG monitoring
- Exclude K from IV fluids
- Start chelation with Lokelma 10g TDS orally up to 72hrs. Rectal calcium resonium per rectum is an alternative if unable to take oral medications (monitoring of calcium levels is required).
- If > 7mmol/l then initiate therapy with 10 units soluble insulin + 50 ml 50% dextrose over 30 minutes. Patient should be monitored on HDU, haemodialysis should be discussed with renal team.

Poor Urine Output

- If urine output is poor then give IV furosemide 1mg/kg
- If patient is anuric a bolus of furosemide 2-4 mg/kg should be given and discuss with the renal team
- CVP monitoring may be required
- If the patient has intra-abdominal nodal disease then an ultrasound should be performed to exclude hydronephrosis
- Haemodialysis or haemofiltration should be considered for volume overload, uncontrolled acidosis, hyperkalaemia or other metabolic disturbances

References

Tumour lysis syndrome: new therapeutic strategies and classification. *British Journal of Haematology (*2004) 127: 3-11

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Appendix 1

Recommended risk stratification and TLS monitoring in patients with Chronic Lymphocytic Leukaemia undergoing Venetoclax ramp-up dosing.

Tumour burden		Prophylaxis		Blood chemistry monitoring[c,d]
		Hydration[a]	Anti-hyperuricaemics[b]	Setting and frequency of assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80ml/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 ml/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital/Outpatient[e] • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.
[a]Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS.
[e] Managed as outpatient whenever possible with close clinical nurse specialist monitoring.

Recommended TLS monitoring in patients with Acute Myeloid Leukaemia undergoing Venetoclax ramp-up dosing.

Prophylaxis measures listed below should be followed:

All patients should have white blood cell count <25 × 109/l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.

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

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

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

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