Kent and Medway Cancer Collaborative

Guidelines for use of RASBURICASE in Adult Haematology and Oncology Patients

Network Guidance Document

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1.0 INTRODUCTION

RASBURICASE guidelines have been developed in order to have a degree of consistency in the use of rasburicase for the prevention and management of tumour lysis syndrome across Kent and Medway.

2.0 BACKGROUND

Tumour lysis syndrome (TLS) is a very serious and sometimes life-threatening complication of cancer therapy. It can be defined as a constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumour necrosis or fulminant apoptosis. The metabolic abnormalities observed in patients with tumour lysis syndrome include hyperkalaemia, hyperuricaemia, and hyperphosphataemia with secondary hypocalcaemia. These can lead to acute renal failure (ARF). The main principles of TLS are the identification of high-risk patients, initiation of preventive therapy, and early recognition and intervention of its complications.

The current management of TLS includes hydration (usually intravenous), diuretics when indicated and the reduction of serum uric acid levels using the xanthine oxidase inhibitor allopurinol.

Allopurinol inhibits xanthine oxidase thus blocking uric acid formation. Urate oxidase catalyses the enzymic oxidation of uric acid to allantoin, a readily excretable metabolite that is very water soluble. It is an endogenous enzyme in most mammals but not in humans. Rasburicase is a recombinant urate oxidase enzyme which is licensed for the “treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in patients with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy”.

3.0 DIAGNOSIS OF TUMOUR LYSIS SYNDROME

Laboratory Screen for TLS

- Urea, Creatinine, Uric acid/Urate, Phosphate, Potassium, corrected Calcium

Cairo-Bishop definition of laboratory TLS

- Laboratory TLS considered present if levels of 2 or more serum values of the following are abnormal at presentation or change by 25% within 3 days before or 7 days after cytotoxic therapy

Urate/Uric acid	>/=476 umol/L or 25% increase from baseline
Potassium	>/= 6.0mmol/l or 25% increase from baseline
Phosphate	>/= 1.45mmol//l or 25% increase from baseline
Corrected calcium	</= 1.75 mmol/l or 25% decrease from baseline

Cairo-Bishop definition of clinical TLS

- Laboratory evidence of TLS plus 1 or more of:
  - Cr >/= 1.5 x ULN
  - Cardiac arrhythmia
  - Seizure

4.0 CRITERIA FOR USE

Rasburicase is to be used immediately prior to and during initiation of chemotherapy only, as at present, there is insufficient data to recommend multiple treatment courses. Rasburicase may be used only for the following indications, when authorised by a Consultant Haematologist or Oncologist:

4.1 Prevention of Tumour Lysis Syndrome

Prior to starting chemotherapy (including steroid monotherapy), the patient's potential to develop TLS must be considered. The assessment takes into account disease type (see tables below), white cell count and additional risk factors, including existing renal dysfunction and signs of TLS.

Individuals with evidence of laboratory TLS at presentation should be treated with full dose rasburicase based on the patient's weight (see table 1).

An individual's risk of tumour lysis should be upgraded (low to intermediate risk, intermediate to high risk) if any one of the following is present (with the exception of individuals with solid tumours or myeloma):

- Pre-existing nephropathy/renal impairment
- Acidosis
- Hypotension
- Prior exposure to a nephrotoxic agent
- Renal involvement by underlying disease process
- Dehydration

Patients allergic to allopurinol should be considered for rasburicase, alternatively patients may be given febuxostat.

Table 1: Prophylaxis based on risk stratification (High risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
High	Laboratory TLS at presentation		Hydration: 2-3L/m^2/day Rasburicase 0.2mg/kg daily until markers of TLS have returned to normal
	Burkitt lymphoma stage III/IV	LDH > 2 x ULN	Hydration: 2-3 L/m^2/day Rasburicase 6mg if no established clinical or laboratory TLS. Dose may be repeated if required. Electrolyte monitoring: every 6-8 hours
	Burkitt leukaemia		
	Lymphoblastic lymphoma stage III/IV	LDH > 2 x ULN	
	ALL	WCC >100 x 10^9/L	
	AML	WCC >100 x 10^9/L	
	T-cell leukaemia/lymphoma, DLBCL, transformed high grade lymphoma, mantle cell lymphoma	Bulky disease	
	CLL	If treated with venetoclax (BCL2 inhibitor)	Follow advice in venetoclax SmPC re electrolyte monitoring, hydration and antihyperuricaemic agents

Table 2: Prophylaxis based on risk stratification (Intermediate risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
Intermediate	Burkitt lymphoma early stage	LDH < 2 x ULN	Hydration: 2-3L/m^2/day Rasburicase 3mg if uric acid >/=476umol/L Allopurinol 300mg/day for 7 days (or until risk of TLS has been resolved) if uric acid < 476 umol/L Electrolyte monitoring recommended every 8-12 hours. However, for outpatients, the frequency of monitoring should be determined on an individual patient basis as clinically indicated.
	T-cell leukaemia/lymphoma, DLBCL, transformed high grade lymphoma, mantle cell lymphoma	ULN < LDH < 2 x ULN, non-bulky	
	Lymphoblastic lymphoma stage I/II	LDH < 2 x ULN	
	ALL	WCC < 100 x 10^9/L and LDH < 2 x ULN	
	AML	WCC 25 – 100 x 10^9/L or LDH > 2 x ULN	
	CLL	If treated with CD 20 antibody (e.g. Rituximab, Obinutuzumab) or fludarabine AND WCC > 50 x 10^9/L	
	CML	If experiencing an accelerated blast crisis	

Table 3: Prophylaxis based on risk stratification (Low risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
Low	Indolent NHL		Oral hydration and close monitoring of fluid status. Electrolyte monitoring: every 12-24 hours. Low threshold for recourse to IV fluids and consideration of allopurinol.
	Adult anaplastic large cell lymphoma (ALCL)		
	Adult intermediate-grade NHL	LDH < 1 x ULN	
	Lymphoblastic lymphoma stage I/II	LDH < 2 x ULN	
	Hodgkin lymphoma (most patients)		
	AML	WCC < 25 x 109/L and LDH< 2 x ULN	
	CLL (most patients)	WCC<50 x 109/L; treated with alkylating agents	
	Multiple myeloma (in the absence of other risk factors)		
	Most solid tumours		

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.

4.2 Treatment of Established TLS

The management of established TLS requires a multidisciplinary approach with involvement of haematologists, nephrologists and intensive care physicians. This refers to situations where chemotherapy has been given and there is evidence of laboratory TLS, with or without clinical TLS, as defined on pg 3.

NB Hyperuricaemia alone is NOT an indication for rasburicase rather than allopurinol if there are no other metabolic abnormalities.

General measures include:

- Ensure vigorous hydration to maintain urine output > 100ml/m^2/hr
- Ensure management of high potassium, according to local guidelines, which should include continuous cardiac monitoring.
- In the absence of contraindications, initiate rasburicase at a dose of 0.2mg/kg/day. The duration of treatment should be determined by clinical response.
- 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 a concurrent high phosphate because of the risk of insoluble calcium phosphate deposition in the renal tubules. Only symptomatic hypocalcaemia should be corrected.
- Moderate/asymptomatic hyperphosphataemia may be treated using local guidelines, usually with hydration and maintenance of high urine output. Uncontrolled hyperphosphataemia is an indication for dialysis.
- Alkalinisation of urine is not recommended when using rasburicase, as in contrast to uric acid, the levels of which will be reduced by the rasburicase, phosphate is more soluble in an acid medium and therefore there is an increased risk of calcium phosphate precipitation in the kidney if the urine is alkalinised.

5.0 DOSE, ADMINISTRATION AND DURATION OF TREATMENT (FULL LIST SEE SPC)

5.1 Dose and Duration

Prevention of TLS

Rasburicase 3mg (fixed dose) as a single dose for intermediate risk patients and 6mg (fixed dose) for high risk patients. A repeat dose may be required after monitoring of clinical and biochemical parameters.

For patients with laboratory TLS at presentation 0.2mg/kg/day should be given.

Treatment of established TLS

0.2mg/kg/day given once daily for 3 to 7 days, until there is a normalisation of uric acid, renal function and electrolytes.

All doses to be given as an intravenous infusion in 50ml Sodium Chloride 0.9% over 30 minutes.

5.2 Administration

Rasburicase should be administered under the supervision of a physician trained in chemotherapy of haematological malignancies.

Administration of rasburicase does not require any change in the timing or scheduling of cytoreductive therapy.

Rasburicase should be infused through a different line than that used for chemotherapeutic agents to prevent any possible drug incompatibility. If use of a separate line is not possible, the line should be flushed out with saline solution between infusion of chemotherapeutic agents and rasburicase.

No dose adjustment in Renal or Hepatic impairment.

6.0 CONTRAINDICATIONS AND WARNINGS (FULL LIST SEE SPC)

6.1 Contraindications

- Hypersensitivity to uricases
- G6PD deficiency and other metabolic disorders known to cause haemolytic anaemia

6.2 Special Warnings and Precautions for Use

Rasburicase, like other proteins, has the potential to induce allergic responses in humans. Clinical experience with rasburicase demonstrates that patients should be closely monitored for the onset of allergic-type undesirable effects, especially severe hypersensitivity reactions including anaphylaxis. In such cases, treatment should immediately and permanently be discontinued and appropriate therapy initiated.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, **but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.**

There is no data available to recommend the sequential use of rasburicase and allopurinol. Allopurinol prevents formation of uric acid, which is the 'substrate' for rasburicase, so there is no rationale for using allopurinol and rasburicase together.

At present, there is insufficient data available on patients being retreated to recommend multiple treatment courses. Anti-rasburicase antibodies have been detected in treated patients and healthy volunteers administered rasburicase.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. **Blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immersed in an ice/water bath. Plasma samples should immediately be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, plasma must be maintained in an ice/water bath and analysed for uric acid within 4 hours.**

7.0 APPROVED PRESCRIBER

Oncology and haematology consultants and SpR's should initiate treatment. SHOs should only prescribe under the instruction of a consultant or SpR.

8.0 REFERENCES

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- Jones, G et al. 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; 169 (15): 661-671 (BCSH guidelines)
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- Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendation for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: An expert TLS panel consensus. Br J Haematol 2010; 149(4): 578-586
- Guidelines for the Management of Tumour Lysis Syndrome in Adults, Royal Surrey NHS Foundation Trust December 2015
- Management of Tumour Lysis Syndrome in Adult Patients. North Cancer Alliance. March 2019

9.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non Surgical Oncology Group

	(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

10.0 DOCUMENT ADMINISTRATION

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