Kent and Medway Cancer Network

Network Guidance Document

Guidelines for use of RASBURICASE in adult Haematology and Oncology patients

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1.0 Introduction

RASBURICASE guidelines have been developed in order to have a degree of consistency across the Kent and Medway Cancer Network (KMCN).

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, urinary alkalisation 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 Criteria for use

Rasburicase is to be used immediately prior to and during initiation of chemotherapy only, as at the 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:

3.1 Prophylaxis at the point of starting chemotherapy

Prophylaxis at the point of starting chemotherapy in the following instances:

- Metabolic Disturbances with a tumour of rapid turnover
    - Uric acid ≥ 0.5mmol/L at the point of the start of chemotherapy.
        - Raised uric acid alone is not a trigger for Rasburicase use, but levels ≥0.5mmol/L at the point of the start of chemotherapy is an indicator of potential problems and merit extreme vigilance
    - Phosphate ≥ 2mmol/L
    - Creatinine > Upper Limit of Normal
        - Rate of change is the most important factor
        - Doubling in a short period of time (e.g. 48 hours) in well hydrated patients and/or Creatinine Clearance of < 60ml/min is an indicator for rasburicase.
    - Potassium ≥ 5.5 mmol/L

If there are a number of metabolic disturbances present, a clinical judgement should be made and treatment initiated earlier where indicated.

- Specific diseases
    - The following recommendations are made with reference to underlying disease
        - Advanced Burkitt’s or Burkitt’s-like lymphoma (stages III & IV)
            - All patients should receive Rasburicase regardless of metabolic disturbances
        - B-ALL, AML, T-PLL, A-TLL, CML blast crisis and T-ALL
            - Patients with these underlying diseases and a WBC > 100 x 10^9/L
        - CLL with metabolic disturbances especially if using Rituximab when WBC > 25 or 100 x 10^9/L - WBC count is rarely significant in this group of patients.

        - Lymphomas
            - In patients with metabolic disturbances listed above.
- High tumour burden
    - It is recommended that tumour burden with low grade disease apart from a very raised WBC should NOT be used as an indicator for rasburicase as it is too difficult to define an appropriate level of tumour burden. LDH is not practical to use as an indicator for rasburicase.
    - However High grade bulky disease +/- high proliferation index (>90% Ki67-MiB-1) may be considered an indicator.

3.2 Rescue or intervention treatment

This refers to situations where chemotherapy has been given and there is evidence of ATLS with hyperuricaemia.

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

Rescue treatment is indicated for the following patients with hyperuricaemia:

- Creatinine > Upper Limit of Normal (as above)
    - Presence of oliguria despite adequate hydration
    - Phosphate ≥ 2mmol/L
    - Potassium ≥ 5.5 mmol/L
    - Hypocalcaemia

- Others:
    - Allopurinol allergy is an indicator for rasburicase
    - Patients may be given febuxostat

4.0 Dose, administration and duration of treatment (full list see SPC)

4.1 Dose

0.2mg/kg/day, given as an infusion in 50ml Sodium Chloride 0.9% over 30 minutes.

4.2 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.

4.3 Duration of treatment

The usual treatment duration is 2 days and most patients will not require more than 3. However, up to 7 days may be given if necessary depending on clinical circumstances. The patient's metabolic function should be monitored closely and used to guide treatment duration along with the clinical evaluation of the disease.

5.0 Contraindications and warnings (full list see SPC)

5.1 Contraindications

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

5.2 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.**

6.0 Approved Prescriber

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

7.0 References

Summary of Product Characteristics for Rasburicase updated 23rd January 2008
Guidelines for the use of rasburicase in the management of Tumour Lysis Syndrome, Consensus Opinion Chair Professor David Lynch UCH, London
Prescribing and administration guidelines for the use of rasburicase, Mount Vernon Cancer Network July 2004
Management of Tumour Lysis Syndrome NLCN Non-Hodgkins Lymphoma guidelines Nov 2005

Document Administration

Approval Record

Approval		
Date	**Name / Title**	**Signature**
April 2008	Maadh Aldouri Chair of HOG (Haematology Non-surgical oncology sub-group)	
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Document Location

The document is located in the Kent and Medway Cancer Network office, in hardcopy and electronic format.

DATE OF NEXT REVIEW

This item is next to be reviewed by September 2013

Revision History

Date	Version	Status	Author	Summary of Changes
March 2008	V4	draft	S Lightfoot	
April 2008	V5	draft	S Lightfoot	Comments of HOG incorporated
May 2008	V5	Final published	S Lightfoot (P Jackson/C Waters incorporated into Network template)	Incorporated into Network template
September 2011	V6	Final	HOG	

MEASURES ADDRESSED BY THIS EVIDENCE ITEM

This item of evidence is submitted against the following measures:

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ORIGINATORS OF THIS EVIDENCE ITEM

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