Guidelines for the Management of Tumour Lysis Syndrome

1. 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).

2. Tumour Lysis Syndrome - Definitions

2.1 Laboratory TLS (Cairo M. & Bishop M. Br J Haematol 2004; 127: 3-11)

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 or 7 days after cytotoxic therapy:

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid*</td>
<td>≥ ULN or 25% increase from baseline</td>
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<tr>
<td>Potassium</td>
<td>≥ 6.0 mmol/l or 25% increase from baseline</td>
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<tr>
<td>Phosphate</td>
<td>≥ 1.45 mmol/l or 25% increase from baseline</td>
</tr>
<tr>
<td>Albumin corrected Calcium</td>
<td>≤1.75 mmol/l or 25% decrease from baseline</td>
</tr>
</tbody>
</table>

*Not included if Rasburicase has been administered within previous 24 hours

2.2 Clinical TLS (Cairo M. & Bishop M. Br J Haematol 2004; 127: 3-11)

Laboratory evidence of TLS plus 1 or more of:

- Creatinine >1.5xULN
- Cardiac arrhythmia or sudden death
- Seizure

3. Prevention of TLS
TLS can develop rapidly and is difficult to treat once established. 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.

3.1 Pre-treatment Biochemical assessment and TLS Screen
This should be requested via CRS and needs to include:
- Urea
- Creatinine
- Uric acid
- Phosphate
- Potassium
- Albumin
- Corrected Calcium
- LDH
- Consider baseline G6PD screen in an ‘at risk’ patient

3.2 Risk stratification requires:
- Disease subtype
- Treatment planned for CLL
- Assessment of bulk for lymphoma or solid tumour
- WBC for leukaemia
- LDH
- Biochemical values of urate, K, phosphate
- Renal function or evidence renal infiltration
<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>Baseline risk score</th>
<th>Upgrade if the following are present</th>
<th>Renal dysfunction or involvement</th>
<th>Raised urate, K or PO4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Majority of cases</td>
<td>Low</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>• Bulky Germ cell, neuroblastoma or SCLC</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Myeloma</strong></td>
<td>Low</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CML CP</strong></td>
<td>Low</td>
<td></td>
<td>Int</td>
<td>-</td>
</tr>
<tr>
<td><strong>CLL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alkylators alone</td>
<td>Low</td>
<td></td>
<td>Int*</td>
<td>-</td>
</tr>
<tr>
<td>• Targeted/biological Rx</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>AML or CML My-BC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• WBC &lt;25 LDH &lt;2 ULN</td>
<td>Low</td>
<td></td>
<td>Int</td>
<td>-</td>
</tr>
<tr>
<td>• WBC &lt;25 LDH ≥2 ULN</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>• WBC 25-100</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>• WBC ≥100</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ALL or CML Ly-BC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• WBC &lt;100 LDH &lt;2 ULN</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>• WBC &lt;100 LDH ≥2 ULN</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>• WBC ≥100</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Burkitt leukaemia</strong></td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Burkitt lymphoma or lymphoblastic lymphoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stage 1-2 LDH &lt;2 ULN</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>-</td>
</tr>
<tr>
<td>• Stage 1-2 LDH ≥2 ULN</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>• Stage 3-4</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hodgkin, SLL, Follicular, Marginal, MALT, Mantle (non-blastoid), CTCL</strong></td>
<td>Low</td>
<td>Int*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>ALCL - adult</strong></td>
<td>Low</td>
<td></td>
<td>Int*</td>
<td>-</td>
</tr>
<tr>
<td><strong>ATLL, DLBCL, PTCL, Transformed disease, Mantle cell (blastoid)</strong></td>
<td>Low</td>
<td>Int*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>• LDH ≤ ULN</td>
<td>Low</td>
<td></td>
<td>Int*</td>
<td>-</td>
</tr>
<tr>
<td>• LDH &gt; ULN Non-bulky</td>
<td>Int</td>
<td></td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>• LDH &gt; ULN Bulky</td>
<td>High</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*RISK STRATIFICATION* (Cairo *et al*. *Br J Haematol* 2010; 149: 578-86)
3.3 Rasburicase

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.

**Dose:** 0.2mg/kg    each dose to be prescribed on stat side and dose banded

<table>
<thead>
<tr>
<th>Patient weight (kg)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 - 41</td>
<td>7.5mg</td>
</tr>
<tr>
<td>41 - 49</td>
<td>9mg</td>
</tr>
<tr>
<td>49 - 56</td>
<td>10.5mg</td>
</tr>
<tr>
<td>56 - 64</td>
<td>12mg</td>
</tr>
<tr>
<td>64 - 71</td>
<td>13.5mg</td>
</tr>
<tr>
<td>71 - 79</td>
<td>15mg</td>
</tr>
<tr>
<td>79 - 86</td>
<td>16.5mg</td>
</tr>
<tr>
<td>86 - 94</td>
<td>18mg</td>
</tr>
<tr>
<td>94 - 101</td>
<td>19.5mg</td>
</tr>
<tr>
<td>101 - 109</td>
<td>21mg</td>
</tr>
</tbody>
</table>

**Instructions for Dilution and Suitable Diluent:** Should be diluted in 50ml Sodium Chloride 0.9%

**Method and Rate of Administration:** The diluted solution should be administered over 30minutes.

No dose adjustment required for renal or hepatic impairment.

Rasburicase is contra-indicated in patients with G6PD deficiency. This condition is X-linked and so is rare in females. There is a geographical association shown in the map below. There may be clinical suspicion of this condition with a family history, a personal history of neonatal/childhood jaundice, laboratory evidence of red cell haemolysis or a film compatible with G6PD deficiency. Despite this contraindication, clinical urgency may preclude holding back the use of Rasburicase until a G6PD screen result is available.
World distribution of G6PD deficiency population gene frequencies. (Scriver et al., 7th ed. McGraw- Hill, Inc.)

3.4 Prevention - Management according to Risk

3.4.1 High Risk Patients
- If possible, consideration should be given to delaying initiation of chemotherapy for 24 – 48 hours whilst supportive measures are initiated.
- Unless there is oliguria or acute renal dysfunction - Hydrate at 3L/m²/day in the first 24 hours prior to chemotherapy with intravenous fluids.
- Aggressive oral hydration with close monitoring (and switch to iv if concerns) may be appropriate for selected patients on a consultant-decision basis.
- If the patient can excrete the water load, greater volumes may be administered up to 4.5L/m²/day.
- Strict fluid balance is required.
- Monitor potassium - ideally plasma potassium should be between 3 - 3.5mmol/L at the start of chemotherapy. Replace cautiously
- Diuretics (furosemide, mannitol) may be required to maintain urine output >100ml/m²/hour.
- Rasburicase to be given - 1 dose prescribed on stat side of drug chart
- Allopurinol should be stopped
- Consider warning ITU/Renal medicine about the need for potential haemofiltration or dialysis

TLS screen at +4 hours, +12 hours and +24 hours as a minimum and then at least once daily thereafter for 3 – 5 days.
**TLS Screen**
This should be requested via CRS and needs to include:
- Urea
- Creatinine
- Uric acid*
- Phosphate
- Potassium
- Albumin
- Corrected Calcium

*A serum urate level can typically only be obtained prior to the patient receiving Rasburicase, however a serum sample taken urgently to the lab on ice can give an informative result if required.

At + 24hrs
- If no laboratory or clinical TLS apparent Rasburicase can be stopped and allopurinol started
- If TLS develops treat as below

### 3.4.2 Intermediate risk patients
- Allopurinol should ideally be commenced at least 24 hours prior to chemotherapy (300-600mg od, adjusted for renal function) N.B. Rasburicase may be considered for patients with severe hypersensitivity to allopurinol.
- Hydrate intravenously at 3L/m^2/day.
- Aggressive oral hydration with close monitoring (and switch to iv if concerns) may be appropriate for selected patients on a consultant-decision basis.
- Diuretics (furosemide, mannitol) may be required to maintain urine output >100ml/m^2/hour.
- Continue high fluid intake for at least 48 hours after starting chemotherapy.
- Once chemotherapy has commenced a TLS screen should be undertaken at approximately +4 hours and repeated the following day as a minimum.
- Rasburicase to be started only if laboratory or clinical TLS develops
- Patients with Int* can be treated with oral hydration and no further monitoring if no additional risk factors for TLS (i.e. high tumour burden, high Ki-67, aggressive chemotherapy) are present on a consultant-decision basis

### 3.4.3 Low risk patients
- Commence allopurinol prior to chemotherapy - usual dose 300mg od, adjusted for renal function.
4. Treatment of TLS ± clinical TLS

- Ensure vigorous hydration
- Ongoing biochemical monitoring twice daily as a minimum until TLS normalised
- Seek ICU/Renal specialist advice as haemofiltration or dialysis may be required.

- Use of Rasburicase
  - Laboratory TLS alone should receive 2 doses in total
  - Clinical TLS should be decided on a case by case basis but a minimum of 2 and a maximum of 5 doses of Rasburicase is recommended

- Allopurinol should be stopped when Rasburicase is commenced and restarted when Rasburicase is stopped
- Alkalisation 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 with alkaline urine. However, alkalisation may be considered if Rasburicase is not available and the patient is severely acidic.

- Correction of high plasma [potassium] according to local guidelines
- Correction of low plasma [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 or asymptomatic hyperphosphataemia may be initially treated by maintaining adequate hydration and use of an oral phosphate binder e.g. Calcichew. However, a renal specialist should be notified regarding the patient in case dialysis is required.
Risk Stratify as per Table 1

- **LOW**
  - Allopurinol
  - TLS screen +4h
  - TLS screen +24h

- **INT**
  - Allopurinol
  - TLS screen +4h
  - TLS screen +12h
  - TLS screen +24h

- **HIGH**
  - Rasburicase – Dose #1
    - TLS screen +4h
    - TLS screen +12h
    - TLS screen +24h

Low TLS:
- Continue allopurinol

TLS Rasburicase – Dose #1
- TLS screening

No TLS:
- Stop Rasb
- Start allopurinol

Lab TLS alone:
- Dose #2 then stop Rasb
- Start allopurinol

Clinical TLS:
- Clinical review
- 2 doses may be adequate
- Maximum 5 doses

*Originally authored by: Dr Matthew Smith from a Barts Health Guideline
Reviewed for London Cancer by: Simon Jenkinson
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