TUMOR LYSIS SYNDROME IN THE CONTEXT OF EMERGING ANTI-CANCER THERAPIES

CAPHO 2018

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I have received honoraria from the following companies:
Advisory Board – Jazz Pharmaceuticals
Educational Program Speaker – Apobiologix, Lundbeck
Honoraria for this presentation from CAPHO
I have no other conflicts of interest to declare

LEARNING OBJECTIVES

► Describe the clinical manifestations and laboratory values which may indicate tumor lysis syndrome (TLS)
► Identify patients who may be at risk for treatment-related TLS
► Tailor therapies for TLS based on individual patient characteristics (including fixed-dose rasburicase)
► Be comfortable discussing the risk of developing TLS with patients and family members

OUTLINE

► Define TLS (laboratory and clinical)
► Review risk factors for TLS
► Discuss prevention strategies and at what stage they should be employed
► Treatment options and the supporting evidence
► Risk and management of TLS associated with new anticancer agents (e.g. venetoclax)
► Pharmacist role in TLS prevention and management

TUMOR LYSIS SYNDROME

CAIRO AND BISHOP

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DEFINITION OF TUMOR LYYSIS SYNDROME

Laboratory TLS occurs in a patient with cancer undergoing treatment within 3 days prior to and up to 7 days post initiation of therapy.

- Uric acid: ≥ 476 umol/L or 25% from baseline
- Potassium: ≥ 6 mmol/L or 25% from baseline
- Phosphate (children): ≥ 2.1 mmol/L or 25% from baseline
- Calcium: ≤ 1.75 mmol/L or 25% from baseline

Clinical TLS occurs in a patient with laboratory TLS and at least one of the following:
- Creatinine: ≥ 1.5 x ULN
- Cardiac arrhythmia
- Sudden death

CRITIQUE OF CAIRO AND BISHOP

- May not have two or more abnormalities present at once, one may precede the other
- 25% change from baseline might not be significant
- Defining AKI on the basis of creatinine > 1.5 x ULN does not clearly distinguish CKD from AKI
- Cannot be applied to spontaneous TLS, which can occur with high risk malignancies

ELECTROLYTE ABNORMALITIES AND CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Electrolyte Abnormality</th>
<th>GI</th>
<th>Neuro</th>
<th>CV</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>_diaheaa, nausea, vomiting, anorexia</td>
<td>_weakness, paresthesias, muscle cramps</td>
<td>_bradycardia, ventricular tachycardia, ventricular fibrillation, asystole, cardiac arrest, ECG changes</td>
<td>_oliguria, anuria, azotemia, renal insufficiency</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>_nausea, vomiting, diarrhea, anorexia</td>
<td>_renal: edema, flank pain, hematuria, oliguria, anuria, azotemia, cloudy urine, crystalluria</td>
<td>_general: lethargy</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>_nausea, vomiting, diarrhea, anorexia</td>
<td>_renal: edema, flank pain, hematuria, oliguria, anuria, azotemia, cloudy urine, crystalluria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>_muscle twitching and cramping, grimacing, tetany, laryngospasm, paresthesias, convulsions, impaired memory, confusion, delirium, hallucination</td>
<td>_general: lethargy</td>
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</tbody>
</table>

RISK STRATIFICATION

**Step 1**
Assess evidence of laboratory or clinical TLS at diagnosis

**Step 2**
Assess whether tumor itself confers high risk

**Step 3**
Assess other risk factors that impact the risk of developing TLS
- Pre-existing renal dysfunction
- Advanced age
- Tumor with renal involvement
- Efficacy of proposed treatment
- Use of predisposing concomitant medications

GUIDELINES

- May not have two or more abnormalities present at once, one may precede the other
- 25% change from baseline might not be significant
- Defining AKI on the basis of creatinine > 1.5 x ULN does not clearly distinguish CKD from AKI
- Cannot be applied to spontaneous TLS, which can occur with high risk malignancies

TUMOR LYYSIS SYNDROME INCIDENCE AND OUTCOMES

- Prevalence
  - Incidence 3-8% (clinically significant)
- Morbidity
  - ~ 1/3 of affected patients require dialysis
- Mortality
  - > 15% mortality rate
### COMPARISON OF HIGH RISK FEATURES

<table>
<thead>
<tr>
<th>British - 2015</th>
<th>NCCN - 2014</th>
<th>Italian - 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned to have intensive chemo and fulfill the following:</td>
<td></td>
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</tr>
<tr>
<td>• ALL or AML with WBC &gt; 100x10⁹/L</td>
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</tr>
<tr>
<td>• Burkitt lymphoma or lymphoblastic lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-grade lymphoma (DLBCL and T-cell NHL) with bulky disease (LDH &gt; 2x ULN)</td>
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</tr>
<tr>
<td>• Hematological diagnosis plus renal impairment or allergy to allopurinol could be considered for rasburicase</td>
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<td></td>
</tr>
<tr>
<td>• Burkitt lymphoma or lymphoblastic lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Occasionally DLBCL and CLL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Spontaneous TLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elevated WBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-existing elevated uric acid (LDH &gt; 10cm diameter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ineffectiveness of allopurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Renal disease or renal involvement by tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AML with WBC &gt; 25x10⁹/L</td>
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### COMPARISON OF MANAGEMENT

<table>
<thead>
<tr>
<th>British</th>
<th>Italian</th>
</tr>
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<tbody>
<tr>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Monitor (fluid status and lab values)</td>
<td>Monitor (hydration)</td>
</tr>
<tr>
<td>Low threshold for HFP</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Consider allopurinol</td>
<td>Monitor (hydration)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Increased hydration, post-initiation of treatment or until risk resolved</td>
<td>Monitor (hydration)</td>
</tr>
<tr>
<td>If sustained and progressive hyperuricemia develops</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>High risk</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Increased hydration</td>
<td>Monitor (hydration)</td>
</tr>
<tr>
<td>Prophylaxis with rasburicase</td>
<td>Rasburicase</td>
</tr>
</tbody>
</table>

### NCCN – NON-HODGKIN’S LYMPHOMAS

- Rigorous hydration
- Manage hyperuricemia
- Frequent monitoring
- Allopurinol starting 2-3 days before treatment and for a duration of 10-14 days
- Rasburicase
  - If high-risk features
  - Urgent need for chemotherapy in a patient with high bulk disease
  - If adequate hydration is difficult or not possible
  - Acute renal failure

### STEPSWISE APPROACH

- First Step
  - Prophylaxis
  - Prevention/Prophylaxis
- Second Step
  - Rasburicase
  - Prevention/Prophylaxis
- Third Step
  - Rasburicase
  - Prevention/Prophylaxis
PREVENTION

- Hydration
  - 2-3L/m²/day
- Urinary alkalinization
  - No longer recommended – may cause precipitation and deposition of calcium-phosphate complex in the renal tubules
- Allopurinol/febuxostat
  - 7 days after initiation of chemotherapy

PROPHYLAXIS

- Initial treatment, re-induction or salvage chemotherapy
- Allopurinol is rarely given for >7 days
- 300-400mg/m²/day of allopurinol for adults
  - Flat dose of 300mg po daily often used
- Renal failure is not a reason to adjust dose
- Continue if patient on allopurinol or febuxostat for gout

FEBUXOSTAT

- Xanthine oxidase inhibitor
- Advantage – less chance of hypersensitivity reactions, hepatic metabolism
- Disadvantage – cost ($2.03/tab)
- Florence trial
  - Compared to allopurinol for TLS: lower uric acid levels but no significant difference in serum creatinine change

APPROACH TO TREATMENT

- Eliminate pharmacotherapy that may contribute
- IVF
- Manage electrolyte abnormalities
  - Hyperkalemia
  - Hyperphosphatemia
  - Hyperuricemia
  - Hypocalcemia
**APPROACH TO TREATMENT**

- Eliminate pharmacotherapy that may contribute
- IVF
- Manage electrolyte abnormalities
  - Hyperkalemia
  - Hyperphosphatemia
  - Hyperuricemia
  - Hypocalcemia – correction NOT recommended unless cardiac arrhythmias are present

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**RASBURICASE**

- $129/1.5mg vial for intravenous administration
- (Allopurinol 300mg tab = $0.08)
- Monograph dosing for 70kg patient:
  - 0.20mg/kg x 70kg = 14mg
  - ~10 vials = $1290/day
  - 7 days = $9030

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**RASBURICASE ADVERSE REACTIONS**

- Rash 23.4%
- Diarrhea 19.4%
- Fever 37.5%
- Headache 25.3%
- Nausea 30.9%
- Vomiting 46.6%
- Methemoglobinemia rare

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**TRIAL 1 – MULTICENTER PHASE THREE TRIAL**

- N = 275
- Inclusion:
  - Age ≥ 18
  - ECOG of 0-3
  - Life expectancy of > 3 months
  - Active leukemia/lymphoma and high or potential risk for TLS

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**TRIAL 1 – TREATMENT ARMS**

| Arm 1 | Rasburicase 0.2mg/kg/day IV for 5 days |
| Arm 2 | Rasburicase 0.2mg/kg/day IV for days 1-3 then allopurinol 300mg po daily days 3-5 |
| Arm 3 | Allopurinol 300mg po daily days 1-5 |
TRIAL 1 - OBJECTIVES
▶ Primary objective: compare the adequacy of plasma uric acid control between the three treatment arms and to evaluate safety
▶ Primary efficacy measure: rate of plasma uric acid response

TRIAL 1 - RESULTS
▶ Plasma uric acid response rate (success defined as plasma uric acid ≤ 7.5mg/dL [446umol/L] for all measurements day 3-7)
  • Rasburicase alone – 87% (95% CI, 80-94%)
  • Rasburicase plus allopurinol – 78% (95% CI, 70-87%)
  • Allopurinol alone – 66% (95% CI, 56-76%)
  • P = 0.001

TRIAL 1 - CONCLUSIONS
▶ Well tolerated and safe (rasburicase) and significantly better than allopurinol in controlling plasma uric acid in terms of rapidity and efficacy
▶ The FDA approved the use of rasburicase for prevention of TLS in high-risk patients based on the results of this study

TRIAL 2 - META-ANALYSIS OF EFFICACY AND COST OF SINGLE DOSE RASBURICASE
▶ 10 studies
▶ Inclusion
  • English
  • RCTs, prospective cohort studies, case-control studies, case series studies
  • Adult patients with cancer for prophylaxis of high-risk TLS or treatment of hyperuricemia
▶ Treatment: varied, weight based dosing (0.05-2mg/kg) and fixed doses (3, 4.5, 6 and 7.5mg)
▶ Endpoints: Response rate, uric acid timeline analysis, dose analysis and cost analysis

TRIAL 2 - RESULTS
▶ Response rate analysis: not significantly different between SDR (single dose rasburicase) and DDR (daily dose rasburicase)
▶ Single dose regimen (SDR) vs daily dose regimen (DDR):
  • SDR group controlled plasma uric acid below 4 mg/dL (238 umol/L) at 24, 48 and 72 hours
  • DDR group had steeper control of plasma uric acid levels
▶ Single dose low v standard:
  • Low-dose SDR group (3mg fixed vs. 0.05mg/kg) - failed to control plasma UA below 4mg/dL at 24 hours
  • Standard-dose (6-7.5mg fixed vs 0.15-0.2mg/kg) - plasma UA maintained below 4mg/dL at 24, 48 and 72 hours
▶ Cost analysis: Standard SDR regimen achieved similar response with substantial savings
TRIAL 2 - CONCLUSIONS

▶ SDR for adults with hyperuricemia or high risk for TLS demonstrated better response rate and faster and stronger control of plasma UA when compared with allopurinol
▶ Pooled response rates of SDR were not inferior to DDR
▶ When using lower dose SDR patients with high risk TLS should be closely monitored because an additional dose may be required

TRIAL 3 – RCT OF SINGLE DOSE RASBURICASE VS FIVE DAILY DOSES

▶ N = 82
▶ Randomized, controlled open label (randomized 1:1 into arm A or B)
  ▪ A = single dose of rasburicase (0.15mg/kg) on day 1
  ▪ B = rasburicase (0.15mg/kg) daily for 5 days
▶ Inclusion:
  ▪ Hematological malignancies
  ▪ ECOG 0-3
  ▪ Life expectancy > 3 months
  ▪ High risk or potential risk for TLS

TRIAL 3 – ENDPOINTS/RESULTS

▶ Primary endpoint: plasma UA response rate – normalization
▶ Findings:
  ▪ Arm A (single dose) UA response was 85% (34 of 40 patients)
  ▪ 100% in potential risk group
  ▪ 71.4% in high risk group (5 required a second dose)
  ▪ Arm B (daily dose) UA response was 98%
  ▪ 100% in potential risk group
  ▪ 95% in high risk group
▶ Adverse events were mild to moderate in severity, and lower in single dose arm as compared to daily dose arm
  ▪ Nausea 12.5% vs 32.5%
  ▪ Constipation 15% vs 32.5%
  ▪ Diarrhea 5% vs 12.5%
  ▪ Vomiting 0% vs 15%

TRIAL 3 – CONCLUSIONS

▶ All patients at potential risk and majority of high-risk patients responded to a single dose
▶ In patients receiving single dose therapy, monitoring is required as some patients may require a second dose.

CONSIDERATIONS IN EVALUATING THE EVIDENCE

▶ Uric acid levels are used as surrogate end points
▶ No difference has been shown in rates of renal failure, dialysis requirements or death
GUIDELINE POSITION ON RASBURICASE

▶ British (high risk adults) – 3mg IV single fixed dose of rasburicase
  • Children – 0.2mg/kg IV single dose
  • Close monitoring
▶ NCCN – 3-6mg IV single dose usually adequate
▶ Italian consensus – EMA 0.2mg/kg/day for adults and children of US FDA
  0.15-0.2mg/kg/day starting 4-24 hours before antitumor therapy and
  continued for 5 days

JONES et al. Guidelines for the management of tumor lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. BJH. 2015


TLS RISK ASSOCIATED WITH TARGETED THERAPIES

▶ Tyrosine kinase inhibitors
▶ Vascular endothelial growth factor receptor TKIs
▶ Monoclonal antibodies
▶ Immunomodulatory agents
▶ Proteasome inhibitors
▶ Cyclin-dependent kinase (CDK) inhibitors

VENETOCLAX AND TLS

▶ Open-label, multicenter, dose-escalation trial in relapsed or refractory CLL, SLL or NHL
▶ Dose-escalation cohort (n=56)
  • 7 patients had laboratory TLS
  • 3 patients had clinical TLS
    - One patient had acute renal failure requiring dialysis
    - One patient died suddenly
  • Led to the expansion cohort, stepwise ramp-up of dosing

VENETOCLAX – RISK ASSESSMENT

▶ Tumor burden (Step 2)
  • Low: all LN < 5cm AND ALC < 25 x 10^9/L
  • Medium: any LN 5cm to < 10cm OR ALC ≥ 25 x 10^9/L
  • High: any LN ≥ 10cm OR ALC ≥ 25 x 10^9/L AND any LN ≥ 5cm
▶ Other risk factors (Step 3):
  • Renal function (CrCl < 80mL/min)
  • Concomitant use of strong CYP3A4 inhibitors
  • Age
  • Comorbidities
  • Dosing
  • Electrolyte abnormalities (Step 1)

VENETOCLAX – TLS PROPHYLAXIS AND MONITORING

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Prophylaxis</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Oral hydration (1.5-2L) Anti-hyperuricemic agent Outpatient monitoring (K, uric acid, PO₄, Ca and Scr) pre dose, 8-12h and pre-dose at ramp-up</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Oral hydration (1.5-2L) and consider IV Anti-hyperuricemic agent Outpatient monitoring as above Consider hospitalization if CrCl &lt; 80mL/min</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Oral hydration (1.5-2L) and IV (150-250mL/hr) Anti-hyperuricemic agent (consider rasburicase if uric acid is elevated) Monitor labs as above IN HOSPITAL pre-dose, 4, 8, 12 and 24 hours for initial doses (subsequent doses outpatient monitoring pre-dose, 6-8h, 24h)</td>
<td></td>
</tr>
</tbody>
</table>

PHARMACIST ROLE
PHARMACIST ROLE IN TLS

▶ Participate in team approach to risk stratification (1, 2, 3)
▶ Pharmacist - counselling
  • Prevention – hydration, allopurinol adherence
  • Monitoring – signs and symptoms of electrolyte abnormalities
▶ Recommend treatment based on patient factors
▶ Information resource for team regarding the appropriate dose, duration and administration of rasburicase