The Crisis of Cell Lysis: A Review of Tumor Lysis Syndrome

Josh Arnold, PharmD
PGY1 Pharmacy Resident

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Objectives

• Identify the risk factors and pathophysiology of tumor lysis syndrome
• Describe preventative strategies and considerations for patients at risk for tumor lysis syndrome
• Discuss current evidence for treatment and management of tumor lysis syndrome
Pathophysiology

Purine Catabolism

Hypoxanthine

XO

Xanthine

XO

Uric Acid

XO: xanthine oxidase
Pathophysiology

Purine Catabolism

Hypoxanthine

XO

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Uric Acid

XO: xanthine oxidase

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Morbidity and Mortality

• 30-35% of affected patients will require hemodialysis
• Overall mortality rate greater than 15%
• TLS shown to be an independent risk factor for AKI and increased 90-day mortality
• Evaluation of 6-month mortality in those with TLS
  • Without AKI: 21%
  • With AKI: 66%
    • Multivariable adjustment: $P = 0.0006$

## Cairo-Bishop Classifications

<table>
<thead>
<tr>
<th>Metabolic Abnormality</th>
<th>Criteria for Laboratory TLS</th>
<th>Criteria for Clinical TLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia</td>
<td>&gt;8.0 mg/dL or 25% increase from BL</td>
<td>-</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>&gt;4.5 mg/dL in adults or &gt;6.5 mg/dL in children or 25% increase from BL</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>&gt;6.0 mEq/L or 25% increase from BL</td>
<td>Cardiac arrhythmia or sudden death due to hyperkalemia</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt;7.0 mg/dL or 25% decrease from BL</td>
<td>Cardiac arrhythmia, sudden death likely due to hypocalcemia, seizure, or neuromuscular toxicity</td>
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</tbody>
</table>

**Laboratory TLS diagnosis requires:**
Two or more metabolic abnormalities within same 24-hour period

**Clinical TLS diagnosis requires:**
Laboratory tumor lysis syndrome in addition to clinical symptoms

BL: baseline

Cairo et al. BJH 2004;127:3-11
Clinical Presentation

Hyperphosphatemia

- Acute kidney injury
- GI upset
- AMS

Hyperkalemia

- ECG abnormalities
- Cardiac arrest
- Fatigue

Hypocalcemia

- AMS
- Seizures
- Arrhythmias
- Tetany and spasms

Hyperuricemia

- Acute kidney injury
- Crystal nephropathy

AMS: altered mental status
GI: gastrointestinal
ECG: electrocardiogram
UOP: urine output

Risk Factors

Cancer Mass
- Bulky tumor or extensive metastases
  - Blast cell count or LDH
- Organ infiltration by cancer cells
  - Hepatomegaly, splenomegaly
- Bone marrow involvement
- Renal infiltration or outflow-tract obstruction

Cell Lysis Potential

Patient Features

Supportive Care


LDH: lactate dehydrogenase
Risk Factors

- **Cancer Mass**
  - High rate of proliferation of cancer cells
  - LDH as a surrogate marker
  - Cancer-cell sensitivity to anticancer therapy
  - Many hematologic malignancies
  - Intensity of initial anticancer therapy

- **Cell Lysis Potential**

- **Patient Features**

- **Supportive Care**


LDH: lactate dehydrogenase
Risk Factors

Cancer Mass

Cell Lysis Potential

Patient Features

Supportive Care

- Nephropathy before diagnosis of cancer
- Dehydration or volume depletion
- Increased baseline uric acid
- Hypotension
- Exposure to nephrotoxins

Risk Factors

- Cancer Mass
- Cell Lysis Potential
- Patient Features
- Supportive Care

- Inadequate hydration
- Exogenous potassium
- Exogenous phosphate
- Delayed uric acid removal

Risk Assessment

Malignant diseases

Hematological malignancies

Solid tumors

Myeloma

Chronic leukemia

CML (chronic phase)

Therapy using only alkylating agents

Lymphoma

AML/ALL

Targeted and/or biological therapies

LRD

LRD

LRD

LRD

IRD

LRD

IRD


CML: chronic myeloid leukemia
CLL: chronic lymphocytic leukemia
LRD: low risk disease
IRD: intermediate risk disease
HRD: high risk disease
Risk Assessment

• Cancer stage, LDH, WBC

• Likelihood of developing clinical TLS highest at initiation of therapy

• Highest risk cancers include:
  • Advanced Burkitt’s lymphoma/leukemia
  • Acute lymphocytic leukemia with WBC count >100k
  • Acute myeloid leukemia with WBC count >50k
  • Diffuse large B-cell lymphoma
  • Bulky disease

LDH: lactate dehydrogenase
WBC: white blood cell

Case

BK is a 31 yo male (62 kg) recently diagnosed with acute lymphocytic leukemia (ALL) with a baseline WBC count of 104,000. No significant PMH.

Other laboratory values are:

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<table>
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<tbody>
<tr>
<td>SCr</td>
<td>0.8</td>
<td>Uric Acid</td>
</tr>
<tr>
<td>K</td>
<td>4.2</td>
<td>LDH</td>
</tr>
<tr>
<td>Ca</td>
<td>9.1</td>
<td>Phos</td>
</tr>
</tbody>
</table>
How would you classify BK’s risk category?

A. Negligible Risk
B. Low Risk
C. Intermediate Risk
D. High Risk
“An ounce of prevention is worth a pound of cure.”

- Benjamin Franklin
Prevention of TLS

• Significant effort focused on:
  • Prevention of dysrhythmias
  • Prevention of neuromuscular abnormalities
  • Maintaining appropriate renal function

• Uric acid levels and progression to TLS

<table>
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<tr>
<th>UA level</th>
<th>RR</th>
<th>Significance</th>
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<tr>
<td>≥8 vs. 4-8</td>
<td>4.03</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>4-8 vs. &lt;4</td>
<td>11.66</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

• Risk of TLS increased 1.75-fold for every mg/dL increase in uric acid (P < 0.0001)

Hydration

• Crystalloid fluid at rate of 2.5-3 L/m²/day
  • Goal urine output 3-5 mL/kg/hour
  • Normal saline vs. lactated Ringer’s solution

• Aggressive hydration offers several benefits:
  • Promotes excretion of uric acid and electrolytes
  • Decreases calcium-phosphate crystal formation in renal tubules
  • Maintains renal perfusion

• Loop diuretics to facilitate diuresis
Alkalization

- Uric acid solubility increases in alkalotic urine
- No longer recommended
  - Risk of metabolic alkalosis
  - Increases calcium phosphate precipitation
  - Promotes calcium binding to albumin
  - Lack of clear evidence of benefit
  - Xanthine solubility is poor regardless of pH

Urine Alkalization

Allopurinol

• Xanthine oxidase inhibitor
• Initiate prior to radiation or chemotherapy
• 10 mg/kg/day given in divided doses
  • Maximum 800mg
• Reduces clearance of purine-based chemotherapies
• Hypersensitivity reactions

BK is placed on prophylactic measures including allopurinol 300mg twice daily and maintenance fluids running at the equivalent of 3.1 L/m²/day. Electrolytes are WNL but slightly increased. Current urine output is ~1.3 mL/kg/hr.

What is the next step in BK’s prophylactic strategy?
What is the next step in BK’s prophylaxis?

A. Increase allopurinol to 400mg twice daily
B. Add loop diuretic to promote diuresis
C. Begin sodium bicarbonate drip to facilitate urine alkalization
D. Start rasburicase
Rasburicase

- Recombinant urate oxidase
- Dosing
  - Weight-based vs. fixed-dose
- G6PD deficiency
- Dialyzable
- Laboratory considerations
- Cost

Purine Catabolism

Hypoxanthine

Xanthine Oxidase

Xanthine

Xanthine Oxidase

Uric Acid

Rasburicase

Allantoin

G6PD: glucose-6-phosphate dehydrogenase

The rasburicase dosing conundrum

• Package insert:
  • 0.2 mg/kg IV infusion daily for up to 5 days
Rasburicase: fixed-dose vs. weight-based

**Design**
- Single center, retrospective chart review
- Primary outcome: uric acid normalization with 24 hours of rasburicase administration

**Population**
- All adult patients who received rasburicase for prevention or treatment with diagnosis of malignancy
- Some significant heterogeneity between groups

**Intervention**
- Treatment with rasburicase as a single dose (3mg, 6mg, or 7.5mg) or weight-based dosing (mean 0.16 mg/kg)
- Evaluated uric acid level at 24, 48 and 72 hours

**Results**
- No significant difference in primary outcome
  - 92.9% vs 97.6% vs 100% vs 98.0% (P = 0.1238)
- Several risk factors may predict single dose failure
- Significant decrease in SCr across groups

Cost Considerations

- Allopurinol: $18.47
- FD Rasburicase: $3,745.36
- WB Rasburicase: $43,865.87
Allopurinol vs. Rasburicase

Allopurinol AUC_{0-96hr} = 329 \pm 129 \text{ mg/dL} \cdot \text{hr}

Rasburicase AUC_{0-96hr} = 128 \pm 70 \text{ mg/dL} \cdot \text{hr}

\( P < 0.0001 \)

Hyperphosphatemia

• Elevated levels of phosphorus in malignant cells
• Restrict phosphorus intake
• Phosphate binders
  • Calcium formulations preferred
• Refractory hyperphosphatemia will often require renal replacement therapy
  • Calcium phosphorus product at least 70 mg²/dL²
  • Symptomatic hypocalcemia

Hyperkalemia

- Rapid onset
- Acute management requires multimodal approach

- Refractory hyperkalemia will require initiation of renal replacement therapy

IV calcium gluconate  Inhaled albuterol  Insulin + dextrose  IV sodium bicarb  Cation exchange resin

Hypocalcemia

- Result of crystallization with serum phosphorus
  - Risk of precipitation in multiple organs
- Judicious supplementation
  - Not indicated when asymptomatic
- Managed via control of serum phosphorus
  - Often requires initiation of dialysis

Dialysis

• Early conventional HD for hyperkalemia

• Benefits of CRRT:
  • Ongoing liberation of substances from lysing cells
  • Prevention of rebound imbalances
  • Phosphorus clearance is time dependent

• Peritoneal dialysis not recommended

• Continue until adequate recovery of renal function and resolution of electrolyte imbalance

A 22 yo female of Asian descent is admitted to the hospital with newly diagnosed AML (WBC 29,000). Her electrolytes are WNL but uric acid is 7.1 mg/dL. She is determined to be at intermediate risk for TLS and started on IV fluids. Of note, she does not have a G6PD test on file.

What should the next step be in this patient’s care?
What should the next step be?

A. Give rasburicase 0.2 mg/kg dose
B. Give rasburicase 6mg dose
C. Order G6PD testing and start allopurinol
D. Hold antihyperuricemic treatment and titrate fluids to goal urine output
Summary

Assess tumor burden

- Small or localized tumor
  - Negligible risk of clinical TLS

- Moderate tumor burden
  - Assess cell-lysis potential
    - Low risk of clinical TLS
    - Intermediate risk of clinical TLS

- Large/bulky tumor burden
  - Assess cell-lysis potential
    - High risk of clinical TLS

Assess patient presentation

- Minimal risk factors
  - Low risk of clinical TLS

- Many risk factors
  - Intermediate risk of clinical TLS
  - High risk of clinical TLS

Summary

Assess tumor burden

Negligible risk of clinical TLS
- No prophylaxis
- No monitoring

Low risk of clinical TLS
- IV fluids
- Allopurinol
- Daily laboratory tests

Intermediate risk of clinical TLS
- IV fluids
- Allopurinol +/- rasburicase
- Inpatient monitoring
- Laboratory tests every 8-12 hours

High risk of clinical TLS
- IV fluids
- Allopurinol +/- rasburicase
- Inpatient cardiac monitoring
- Laboratory tests every 4-6 hours

Assess cell-lysis potential

Small or localized tumor
Low or medium

Moderate tumor burden
High

Assess patient presentation

Minimal risk factors
Low

Many risk factors
High

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The role of febuxostat

Design
- Randomized, double-blind, phase III trial
- Compare efficacy of febuxostat with allopurinol in serum uric acid level control and preservation of renal function

Population
- ECOG performance group 0-3; sUA level <10 mg/dL
- Hematologic malignancy at intermediate to high risk of TLS

Intervention
- Low, standard and high doses of allopurinol vs. fixed dose febuxostat
- Therapy started 2 days prior and continued for 7-9 days total

Results
- Mean sUA AUC lower on febuxostat (514 vs. 708; P<0.0001)
- No change in SCr level between groups during therapy
- Safety outcomes were similar between groups