Prevention and Treatment of an Oncologic Emergency: Focus on Tumor Lysis Syndrome

Webinar
Tuesday, October 6, 2009
12:00 pm – 1:00 pm (EDT)

Planned and conducted by ASHP Advantage.
Supported by an educational grant from sanofi-aventis.
Prevention and Treatment of an Oncologic Emergency: Focus on Tumor Lysis Syndrome

Webinar Information

How do I register?
Go to the educational initiative website at www.improvingpatientoutcomes.com. Select the “Registration and Program List” page. After locating this live webinar, click the “Register Now” button for the date that is most convenient for you and complete the fields. You will be e-mailed computer and phone connection information.

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A live webinar brings the presentation to you – at your desk, in your home, through a staff in-service. You listen to the speaker presentation in “real time” as you watch the slides on the computer screen. You will have the opportunity to ask questions related to the topic at the end of the activity. In fact, continuing pharmacy education (CPE) credits earned through participation in webinars qualify as live CPE credit and may be counted toward live CPE requirements when renewing your license. Please join the conference at least 5 minutes prior to the scheduled start time for important activity announcements.

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How do I ask a question of the presenter?
Follow the instructions provided at the beginning of the activity for submitting text questions. The speaker will answer as many questions as possible at the conclusion of the activity.

TLS web-based educational activities available at www.ashpadvantage.com/tls

So that this educational activity can be shared with a wider audience, a basic web-based educational activity, Understanding the Basics of Tumor Lysis Syndrome, and a beyond the basics web-based educational activity, Prevention and Treatment of an Oncologic Emergency: Focus on Tumor Lysis Syndrome, are available at www.ashpadvantage.com/tls. Tell your pharmacy colleagues who were unable to attend this program about this free online educational activity!
Prevention and Treatment of an Oncologic Emergency:  
Focus on Tumor Lysis Syndrome

Educational Initiative Program Chairs

Susannah E. Koontz, Pharm.D., BCOP  
Clinical Practice and Education Consultant  
Pediatric Hematology/Oncology and Stem Cell Transplantation  
Houston, Texas

Kamakshi V. Rao, Pharm.D., BCOP  
Oncology Clinical Pharmacy Specialist  
University of North Carolina Hospitals and Clinics  
Chapel Hill, North Carolina

Presentation Faculty

Kamakshi V. Rao, Pharm.D., BCOP  
Oncology Clinical Pharmacy Specialist  
University of North Carolina Hospitals and Clinics  
Chapel Hill, North Carolina

Dr. Kamakshi Rao is an Oncology Clinical Pharmacy Specialist at the University of North Carolina (UNC) Hospitals and Clinics located in Chapel Hill, North Carolina. At UNC, Dr. Rao’s clinical practice focuses in the area of adult bone marrow and stem cell transplantation. She rounds with the multidisciplinary bone marrow transplant team and provides education to medical residents and fellows. Additionally, Dr. Rao serves as co-coordinator for the UNC pharmacy practice residency program and is a preceptor for UNC pharmacy students, PGY1, and PGY2 oncology residents. At UNC, Dr. Rao serves on numerous patient care and oncology focused subcommittees. She is a member of the American Society of Health-System Pharmacists (ASHP), Hematology/Oncology Pharmacy Association (HOPA), and American Society for Blood and Marrow Transplantation (ASBMT). Previously, she worked as an Oncology Clinical Pharmacy Specialist at the Hospital of the University of Pennsylvania. Dr. Rao has served as the Network Facilitator for Oncology in ASHP’s Division of Clinical Specialists and Scientists, participated in and presented at a number of meetings, including ASHP, HOPA, ASBMT, American Society of Hematology (ASH), and American Society of Clinical Oncology (ASCO), and published in numerous journals.

Dr. Rao graduated from Rutgers University College of Pharmacy. She then completed a pharmacy practice residency at the Medical College of Virginia followed by an Oncology Pharmacy Fellowship at The Cancer Institute of New Jersey. She became a Board Certified Oncology Pharmacist in 2003.
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Presentation Faculty

Susannah E. Koontz, Pharm.D., BCOP

Dr. Koontz declares that she has served as a speaker for Genzyme Oncology and Enzon Pharmaceuticals and is an advisory board member for sanofi-aventis.

Activity Planners

Susannah E. Koontz, Pharm.D., BCOP

Dr. Koontz declares that she has served as a speaker for Genzyme Oncology and Enzon Pharmaceuticals and is an advisory board member for sanofi-aventis.

Kamakshi V. Rao, Pharm.D., BCOP

Dr. Rao declares that she has no relationships pertinent to this activity.

Erika L. Thomas, M.B.A, R.Ph.

Ms. Thomas declares that she has no relationships pertinent to this activity.
Prevention and Treatment of an Oncologic Emergency: Focus on Tumor Lysis Syndrome

Activity Overview

As a valued member of the health care team that manages the care of oncology patients, pharmacists are in a key position to impact the care of patients at risk for developing or those that present with oncologic emergencies, including tumor lysis syndrome (TLS). TLS, a group of metabolic abnormalities resulting from the spontaneous or treatment-related rapid breakdown of malignant tumor cells, is a serious and potentially life-threatening medical emergency. When TLS occurs, it is essential that the patient receive prompt medical attention in order to prevent acute complications that can have severe repercussions, including death of the patient.

This program will help pharmacists appropriately identify patients who are at high risk of developing TLS. Monitoring and providing treatment options for patients who develop this medical emergency or those for whom prophylactic therapy is warranted will also be addressed. Case studies will be used to illustrate key concepts.

Activity Learning Objectives

At the conclusion of this application-based CPE activity, participants should be able to:

- Summarize current clinical data regarding the safety and efficacy of agents used for the management of tumor lysis syndrome (TLS).
- Present with a clinical case, design a treatment plan for a patient with TLS and a patient determined to be at high risk for development of TLS.
- Make therapeutic recommendations for prophylaxis and treatment of TLS in patients at risk for its development that include an assessment of the cost effectiveness of various therapeutic alternatives.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE Activity #204-000-08-440-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements of continuing pharmacy education at the ASHP Learning Center at http://ce.ashp.org, following this activity.

Complete instructions for receiving your CPE statement online are on the next page. Be sure to record the five-digit session code announced during this activity.

Target Audience

This continuing education program was planned to meet the needs of pharmacists who practice in oncology or are interested in improving the identification and management of tumor lysis syndrome (TLS).
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Instructions for Processing Continuing Pharmacy Education (CPE)

To obtain your CPE statement of credit for this live activity, please visit the ASHP Learning Center at http://ce.ashp.org.

1. Select "Process Meeting CE" from bottom left. Log in to the ASHP Learning Center using your e-mail address and password.

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2. Once logged in to the site, click on “Process Meeting CE.”

3. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The Activity Code for this meeting is 09616. The Session Code was announced at the end of this activity. Click register again when prompted. When you receive the “thank you for registering” message, click continue. This step will bring you back to your meeting list. Click on the start link to the right of the activity title.

4. Enter the session code, which was announced during the activity, and select the number of hours equal to your participation in the activity. Pharmacists should only claim credit for the amount of time they participate in this activity.

5. Click submit to receive the attestation page.


7. Click on View/Print Statement of Credit next to the meeting name to print your CPE statement.

   Activity code: 09616

   Session code: 

**NEED HELP?** Contact ASHP Advantage at support@ashpadvantage.com.
Prevention and Treatment of an Oncologic Emergency:
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Kamakshi V. Rao, Pharm.D., BCOP
Oncology Clinical Pharmacy Specialist
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Announcements

• Handout is available at http://www.ashpadvantage.com/tls
• Process your CPE online after the webinar at http://ce.ashp.org
• Please complete the brief, eight-question evaluation after this program.
• This webinar is planned and conducted by ASHP Advantage and supported by an educational grant from sanofi-aventis.

Learning Objectives

• Understand how to assess a patient’s risk for developing tumor lysis syndrome (TLS)
• Describe the clinical manifestations and laboratory values suggestive of TLS in at-risk patients
• Summarize current treatment options for the prophylaxis and management of TLS

Introduction

• Tumor lysis syndrome (TLS) is an oncological emergency characterized by severe metabolic derangements
• Destruction of malignant cells leads to rapid release of intracellular contents which can overwhelm the body’s normal homeostatic mechanisms
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Pathophysiology

Etiology and Risk Factors

• Most frequently seen in aggressive lymphomas (Burkitt’s type) and leukemias (ALL)
  – May occur in up to 6% of NHL patients
• Can be seen in almost any tumor type
  – Case reports describe incidences with myeloma, breast cancer, ovarian cancer, SCLC, sarcomas, and germ cell tumors

Etiology and Risk Factors

• Patient Specific Risk Factors
  – Pre-existing renal dysfunction
  – Hypovolemia
• Tumor Specific Risk Factors
  – Increased tumor cell proliferation rate
  – Larger tumor size
  – Chemosensitivity of the tumor

Risk of TLS – Tumor Types

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>* Burkitt’s lymphoma&lt;br&gt; * High-grade non-Hodgkin’s lymphoma&lt;br&gt; * Lymphoblastic leukemia&lt;br&gt; * T-cell acute leukemia&lt;br&gt; * Other acute leukemias</td>
</tr>
<tr>
<td>Moderate</td>
<td>* Low-grade lymphoma treated with definitive therapy&lt;br&gt; * Multiple myeloma&lt;br&gt; * Breast carcinoma treated with chemotherapy/hormonal therapy&lt;br&gt; * Small-cell lung carcinoma&lt;br&gt; * Germ-cell tumors (seminoma, ovarian)&lt;br&gt; * Neuroblastoma</td>
</tr>
<tr>
<td>Low</td>
<td>* Hodgkin’s lymphoma&lt;br&gt; * Low-grade lymphoma treated with interferon&lt;br&gt; * Medulloblastoma&lt;br&gt; * Merkel’s cell carcinoma&lt;br&gt; * Adenocarcinoma of the gastrointestinal tract</td>
</tr>
</tbody>
</table>

Timing of TLS

• Usually occurs within 24 to 48 hours of initiation of therapy
  – Can rarely occur later in treatment course (up to 7 days after therapy initiation)
• Initial courses of therapy pose greatest risk
• Effects may persist for 5-7 days
• Can occur spontaneously

Pathophysiology of TLS


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Clinical Manifestations & Consequences

- Clinical signs and symptoms
  - Gastrointestinal
    - Nausea, vomiting, anorexia, diarrhea
  - Cardiovascular
    - Edema, hypotension, congestive heart failure, arrhythmias, changes in blood pressure, acute myocardial infarction
  - Musculoskeletal/Central Nervous System
    - Lethargy, confusion, mental status changes, pruritus, muscle cramps, tetany, paresthesias, joint pain, back pain, syncope, seizure
  - Renal
    - Oliguria, anuria, cloudy urine, hematuria, renal failure

Hyperuricemia

- Rapid release and catabolism of intracellular nucleic acids (purines)
- Typically occurs 2-3 days after starting therapy
- Uric acid secretion occurs distal to the renal proximal tubule
- High concentrations of uric acid may lead to the formation of uric-acid crystals in the distal tubules and collecting ducts, resulting in obstructive uropathy and uremia

Pathway for Purine Catabolism

Defining TLS

- There are two major scales by which to define TLS
  - Hande & Garrow and Cairo & Bishop
  - Both use similar evaluation criteria
- Laboratory TLS
  - Definition purely by lab parameters
  - Changes in PO4, K, Ca, BUN/SCr, and uric acid
- Clinical TLS
  - Incorporates laboratory criteria and physical symptoms (arrhythmias, sudden death, seizure)

Approaches to the Management of TLS

- Prophylaxis is essential to avoid severe consequences of TLS
  - Hydration
  - Alkalization of the urine
  - Electrolyte Repletion
  - Uric acid reduction
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**Polling...**

**Aggressive Hydration and Diuresis**
- Initiate 24-48 hours prior to and continue for up to 72 hours after chemotherapy
  - Fluid volume ≥ 3-3.6 L/m²/day
  - Reduces serum potassium, phosphate, and uric acid concentrations
- Goals of hydration
  - Urine output > 100 mL/m²/hr (adults)
  - > 3 mL/kg/hr (children)
- If goal not met with just fluids, may use furosemide and/or mannitol to augment effect and tolerability
- Risk of fluid overload (heart failure, renal failure)


**Urinary Alkalization**
- Employed to reduce risk of uric acid crystallization.
- Maintain urine pH 6.5-7.5 to allow solubility of uric acid
  - Relative solubility of urate and xanthine
- Agents
  - Oral acetazolamide
  - Oral sodium bicarbonate
  - IV sodium bicarbonate (WATCH TONICITY OF FLUID)

**Electrolyte Management**
- Intracellular electrolytes are spilled into circulation
  - Hyperkalemia
  - Hyperphosphatemia
- Downstream effects
  - Hypocalcemia
    - Induced by hyperphosphatemia
  - It is critical to aggressively monitor and treat these electrolyte imbalances

**Hyperuricemia**
- Goals of treatment
  - Prevent further formation of uric acid from cell breakdown
  - Decrease amount of circulating uric acid, to decrease risk of uric acid nephropathy
- Options for treatment
  - Allopurinol
  - Rasburicase

**Hyperuricemia - Allopurinol**
- Synthetic structural analog of hypoxanthine
- Inhibits xanthine oxidase, preventing conversion of hypoxanthine and xanthine into uric acid
- Considered gold standard for treatment of malignancy associated hyperuricemia for nearly 50 years

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Allopurinol

- **Dosing:** 100-300mg orally daily
  - **Peds:** 200-300mg/m2/day divided into 1-3 doses
- **Adjustment for renal function**
  - Parent drug (allopurinol)
    - T1/2 1-3 hours
  - Active metabolite (oxypurinol)
    - Active for 18-30 hours

Allopurinol - Toxicity

- Generally well tolerated
- Mild dermatologic reactions occur in 1-10% of patients
- Rare, serious adverse events (<1%)
  - Acute tubular necrosis/interstitial nephritis
  - Agranulocytosis
  - SJS/TEN
- Drug interactions
  - 6-Mercaptopurine and azathioprine
  - Thiazide diuretics and ACE inhibitors

Allopurinol - Drawbacks

- **Limitations**
  - Takes up to 3 days to see effects
  - May result in xanthine nephropathy
  - Delays in initiation of chemotherapy
  - Increased rate of adverse reactions with continued dosing
  - Inability to affect uric acid that has already formed

Rasburicase

- FDA-approved indication
  - Management of uric acid levels in pediatric patients at risk for TLS
- **Dose**
  - 0.15 – 0.2 mg/kg IV daily x 5 days
  - Begin chemotherapy 4 – 24 hrs after the 1st dose
  - No dose adjustments for renal or hepatic dysfunction

Rasburicase

- **Adverse reactions**
  - Skin rash (most common), fever, headache and GI complaints
- No known drug interactions
- **Black box warnings**
  - Anaphylaxis
  - Hemolysis ⇒ Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Methemoglobinemia
  - Interference with Uric Acid Measurements
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Polling...

Interference with Uric Acid Measurements

• Blood specimens for uric acid levels should be placed on ice immediately to prevent further degradation of uric acid ex vivo

Comparison of Allopurinol and Rasburicase

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol</th>
<th>Rasburicase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect on uric acid</strong></td>
<td>Decreases new production</td>
<td>Decreases existing levels</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Days</td>
<td>Hours</td>
</tr>
<tr>
<td><strong>Relative efficacy</strong></td>
<td>Weak</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Several reported (some major)</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
<td>For renal dysfunction</td>
<td>None necessary</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>None</td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td><strong>Black box warnings</strong></td>
<td>None</td>
<td>Four</td>
</tr>
<tr>
<td><strong>Formulations</strong></td>
<td>IV and PO (tablets and extemporaneous suspension)</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Relative cost</strong></td>
<td>Inexpensive</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

Selecting an Agent

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol</th>
<th>Rasburicase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uric Acid Level</strong></td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Tumor Type</strong></td>
<td>Hodgkin's lymphoma</td>
<td>Burkitt's lymphoma, Acute lymphoblastic leukemias</td>
</tr>
<tr>
<td><strong>Tumor Burden</strong></td>
<td>WBC ≤ 25-50 x 10⁹ cells/L, LDH ≤ 2 x normal</td>
<td>WBC &gt; 25-50 x 10⁹ cells/L, LDH &gt; 2 x normal</td>
</tr>
<tr>
<td><strong>Cytoreductive intensity</strong></td>
<td>Less aggressive</td>
<td>More aggressive</td>
</tr>
<tr>
<td><strong>Kidney Infiltration</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Guidelines 2008 Journal of Clinical Oncology

• Evidence-based guidelines developed by adult and pediatric oncologists
• TLS classified based on methodology developed by Cairo and Bishop
• Prevention and management strategies identified with respect to hyperuricemia and to a lesser extent other electrolyte abnormalities
• Mention of monitoring parameters, dialysis and pharmacoeconomics

Guidelines 2008 Journal of Clinical Oncology

• Risk stratification
  – Low
    • Clinical judgment and monitoring
    • Hydration and urine output goals listed
  – Intermediate
    • Hydration + initial management with allopurinol (may consider rasburicase for pediatric patients)
    • If hyperuricemia develops → initiate rasburicase
  – High
    • Hydration + rasburicase
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Guidelines
2008 Journal of Clinical Oncology

- Significant changes from previous recommendations
  - No longer using sodium bicarbonate for alkalization due to potential complications and lack of clear evidence showing a benefit (except in the presence of metabolic acidosis)
  - Once rasburicase is used, allopurinol is not necessarily warranted (based on expert opinion of panel), however ongoing clinical trial will address this issue


Guidelines
2008 Haematologica

- Italian guidelines organized by two chairmen appointing eight members
  - 5 hematologists and 1 oncologist
  - 1 pediatrician and 1 nephrologist
- Key questions identified and all members drafted statements addressing each
  - Scoring of each members statements created the consensus guidelines


Guidelines
2008 Haematologica

- How should TLS be defined and graded?
  - Similar to the Cairo-Bishop method
- How should pre-treatment risk be assessed?
  - Includes host-related, disease-related and therapy-related factors
  - Evaluations prior to chemotherapy should include: CrCl/eGFR and LDH as well as renal ultrasound (for high risk pediatric patients)


Guidelines
2008 Haematologica

- When and which TLS prophylaxis?
  - Recommendations similar to guidelines by Coiffier et al but rasburicase use more aggressive
- Which monitoring approach for TLS?
  - More exhaustive than guidelines by Coiffier et al


Guidelines
2008 Haematologica

- Which TLS therapy/treatment?
  - Similar to guidelines by Coiffier et al
- When are dialytic procedures for TLS appropriate?
  - More detailed information than Coiffier et al guidelines but similar recommendations
- Pharmacoeconomic issues addressed


Rasburicase Dosing Strategies

- FDA approved dosing:
  - 0.15-0.2 mg/kg IV daily for 5 days
  - At $387/1.5mg vial, 5 day dosing for an average 70kg patient (10.5mg)would cost over $13,000.
- Questions
  - Does everyone need 5 days of therapy?
  - Weight based or flat dosing?
  - Who is an appropriate candidate for therapy, considering the cost?
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Rasburicase: Does Everyone Need 5 Days of Therapy?

- **Pui et al**: Evaluation of rasburicase requirements in adult and pediatric patients at high risk for TLS or those with TLS
  - N=245
  - **Results**
    - For those with hyperuricemia on presentation, patients received a median of 3 doses of rasburicase with appropriate drop in uric acid levels
    - For patients treated prophylactically, pediatric patients received an average of 2 doses while adults received an average of 3 doses
    - All maintained uric acid levels within normal limits
    - 10 pediatric patients required dialysis
      - All were for treatment of hyperphosphatemia and azotemia

- **Coiffier B et al.** J Clin Oncol 2003;21:4402-6
  - Pivotal early phase trial of rasburicase in the adult population
    - N=100, 79% with diffuse large B-cell lymphoma
    - Patients received 0.2mg/kg/day of rasburicase for 3-7 days
    - **Results**
      - 100% of patients receiving 3 days of therapy had rapid and dramatic decreases in uric acid levels
      - Included 11 patients who presented with hyperuricemia

- **Liu CY et al.** Leukemia Research 2005;29:463-5
  - **Weight Based Single Dose**
    - Single center study (n=8)
    - Patients included if uric acid > 8mg/dL
    - Treatment
      - 0.15mg/kg rasburicase x 1 dose
      - Based on actual BW if not obese, adjusted body weight if obese
    - Monitoring
      - Uric acid at 12 hours then daily
    - Uric acid levels normalized in all 8 patients
    - No repeat dosing necessary
    - Levels remained normal (<4 mg/dl) for entire 96 hour interval in all patients
    - No HD required

- **McDonnell AM et al.** Pharmacotherapy 2006;26(6):806-812
  - **Flat Dose Efficacy**
    - 11 of 12 patients responded adequately, with decreases in their uric acid and SCr
      - 41 yoM with newly dx AML, uric acid= 17.4 mg/dL
    - Patient weight = 259 kg (height=68 inches)
    - IBW=68.4kg
    - **Treatment**
      - After initial 6mg dose, uric acid dropped from 17.4 mg/dL to 15.4 mg/dL
      - Additional 6mg dose dropped uric acid to 1.4 mg/dL
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**Lowering the Flat Dose**

- Single center study (n=43)
  - Hyperuricemia due to malignancy
  - 15/43 had clinical symptoms of TLS
  - Treated with 3mg flat dose rasburicase
- Results
  - 37/43 patients required only 1 dose to maintain adequate lowering for 48 hours
    - Remaining 6 normalized with second 3-mg dose
    - None of these patients were morbidly obese
- Case reports of success with similar approach recently presented

**But is it economical??**

- Low and moderate risk patients
  - Cost effectiveness evaluation based on drug cost alone, because comparison of rasburicase to traditional therapy not assessed in this population
  - Cost efficacy may exist for patients <10kg if alternative therapy is IV allopurinol
  - For adults or those using PO allopurinol, no cost effectiveness of using rasburicase

**Economic Implications in High Risk Patients**

- Potential cost effectiveness, and even cost-saving, depending on patient weight and number of doses given
- Consider use of other medical resources other than drug
  - Total costs of care are considerably different depending upon development of renal failure and the need for dialysis
    - Renal failure + dialysis: $51,990
    - Renal failure w/o dialysis: $25,575
    - No renal failure: $9,978

**Tumor Lysis Syndrome**

**Patient Case Discussions**

**Patient Case #1**

- WL is a 56 year old male who presented to his PMD with c/o increasing fatigue and SOB. Workup revealed massive lymphadenopathy and a biopsy consistent with diffuse large B-cell lymphoma. He is scheduled to begin chemotherapy emergently.

**Case #1**

- What laboratory studies should be done to evaluate WL’s risk for the development of tumor lysis syndrome?
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Case #1

- Laboratory evaluation
  - Uric acid = 16.8 mg/dL
  - Potassium = 6.1 mEq/L
  - Phosphate = 6.4 mg/dL
  - Calcium = 5.4 mg/dL
  - WBC = 40K/mm³
  - Lactate dehydrogenase = 1265
  - Serum creatinine = 4.5 mg/dL

- What, if any, are WL’s risk factors for developing TLS?

- Patient specific risk factors
  - Pre-existing renal dysfunction
  - High uric acid at presentation

- Tumor specific risk factors
  - Aggressive lymphoma
  - High tumor burden
  - High chemosensitivity
  - renal infiltration

Case #2

- DC is a 35 year old female recently diagnosed with acute myeloid leukemia. On diagnosis, her pertinent labs were:
  - WBC 6.8, 12% blasts
  - SCr 0.8 mg/dL
  - Bone Marrow Bx: 40% blasts in bone marrow

- She has no significant PMH and has been in her usual state of health until this diagnosis
- Her physician plans to start chemotherapy within the next week

- DC’s initial laboratory TLS evaluation
  - Uric acid = 6.4 mg/dL
  - Potassium = 5.1 mEq/L
  - Phosphate = 2.8 mg/dL
  - SCr = 0.8 mg/dL
  - LDH = 220

- Based on patient and tumor related risk factors, is DC at high risk for developing tumor lysis syndrome?
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Case #2

- DC is not at very high risk of developing TLS
  - Her leukemia is not one associated with high rates of TLS. ALL is associated with TLS more than AML
  - She has no other patient specific risk factors predisposing her to the development of TLS

Polling...

Conclusions

- Tumor lysis syndrome is an oncologic emergency with severe consequences if left untreated
- Identification of at-risk patients and preemptive treatment is key to the management and prevention of TLS
- A number of options for pharmacotherapy exist. Appropriate selection of agents is a key role for the practicing pharmacist.
# Prevention and Treatment of an Oncologic Emergency: Focus on Tumor Lysis Syndrome

## Summary of Therapeutic Options to Manage Metabolic Disturbances Associated with Tumor Lysis Syndrome

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Side Effects</th>
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</thead>
<tbody>
<tr>
<td><strong>Hyperkalemia</strong></td>
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<tr>
<td>Calcium gluconate 10%</td>
<td>Stabilizes cardiac membranes</td>
<td>Initial 1-2 gm (4.65-9.3 mEq) /dose IV over minutes with potential for repeat dosing</td>
<td>60-200 mg/kg/dose IV over minutes with potential for repeat dosing</td>
<td>Vasodilation Hypotension Bradycardia Arrhythmias Hypercalcemia</td>
<td>* Rapid onset of action (1-2 minutes) but short acting (10-30 minutes) * May require EKG monitoring * Does not lower serum potassium levels * Risk of calcium-phosphate precipitation * Risk of extravasation and tissue necrosis</td>
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<tr>
<td>Sodium polystyrene sulfonate (Kayexalate®, Kionex®, SPS®)</td>
<td>Binding resin that exchanges sodium for potassium in the GI tract</td>
<td>15-30 gm/dose PO 1-4 times a day or 30-50 gm/dose rectally Q 6 hours</td>
<td>1 gm/kg/dose PO Q 6 hours or 1 gm/kg/dose rectally Q 2-6 hours</td>
<td>Constipation Fecal impaction Intestinal obstruction Nausea Vomiting Hyperkalemia Hypomagnesemia Hypocalcemia Alkalosis</td>
<td>* Variable onset of action – enema has faster onset of action but oral administration has longer duration of action * No systemic effects seen * 1 gm of resin binds approximately 1 mEq potassium * Chilling solution prior to oral administration may improve palatability * Do not mix in orange juice</td>
</tr>
<tr>
<td>Regular insulin (Humulin® R and Novolin® R) and Dextrose</td>
<td>Insulin promotes intracellular shift of potassium and dextrose prevents subsequent hypoglycemia</td>
<td>25-50 gm dextrose/dose IV over 0.5-1 hour combined with 10 units regular insulin IV</td>
<td>0.5-1 gm dextrose/kg/dose IV over 0.5-2 hours combined with regular insulin (insulin dose is 1 unit IV for every 4-5 gm of dextrose given)</td>
<td>Hypoglycemia Hyperglycemia</td>
<td>* Onset is 30-60 minutes with duration of effects 4-12 hours * Considered first-line in symptomatic patients * Do not substitute other insulin products</td>
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<tr>
<td>Loop diuretics (Lasix®, Demadex®, Bumex®)</td>
<td>Renal excretion of potassium in addition to fluids and phosphate is increased through the inhibition of sodium and chloride reabsorption</td>
<td>Furosemide: 20-40 mg/dose IV or 20-80 mg/dose PO Q 6-12 hours</td>
<td>0.5-1 mg/kg/dose IV or 1-2 mg/kg/dose PO Q 6-12 hours</td>
<td>Hypotension Dizziness Headache Hypomagnesemia Hypocalcemia Hypophosphatemia Ototoxicity</td>
<td>* Onset is 5-10 minutes with IV and 30-60 minutes with PO and duration of effects 1-2 hours dependent lasting 2-12 hours * May require IV fluids to avoid dehydration * Monitor blood pressure, electrolytes and renal function</td>
</tr>
<tr>
<td>Sodium bicarbonate (Neut®)</td>
<td>By increasing serum pH, potassium is shifted intracellularly</td>
<td>0.5-1 mEq/kg/dose IV over minutes</td>
<td>0.5-1 mEq/kg/dose IV over minutes</td>
<td>Metabolic alkalosis Hyperkalemia Edema</td>
<td>* Onset is 30-60 minutes with duration of effects 1-2 hours * Reserved for patients with acidosis or EKG changes * Use can lead to calcium-phosphate precipitation * Use with caution in patients with heart failure or renal failure</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Removes serum potassium</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Hypotension Hypomagnesemia</td>
<td>* Reserved for symptomatic patients * Most effective method to decrease serum potassium * Can also be used for hyperphosphatemia</td>
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<td><strong>Hyperphosphatemia</strong></td>
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<td>Aluminum hydroxide</td>
<td>Prevents gut reabsorption of phosphate</td>
<td>500-1800 mg/dose PO 3-6 times/day</td>
<td>50-150 mg/kg/day PO divided Q 4-6 hours</td>
<td>Chalky taste, Stomach cramps, Constipation, Fecal impaction</td>
<td>* Give with meals * Aluminum toxicity is a concern with long-term, especially in patients with renal dysfunction</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>Binds dietary phosphate to form insoluble calcium phosphate which is excreted without being systemically absorbed</td>
<td>2 tablets (1334 mg)/dose PO TID</td>
<td>No information</td>
<td>Nausea, Pruritis, Hypercalemia</td>
<td>* Give with meals * Generally not recommended as it may cause calcium-phosphate precipitation (particularly when urine pH &gt; 7.5)</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>Cationic polymer that binds intestinal phosphate via ion exchange and hydrogen bonding</td>
<td>800-1600 mg/dose PO TID</td>
<td>No information</td>
<td>Nausea, Vomiting, Constipation, Diarrhea, Dyspepsia, Pruritis, Dyspnea</td>
<td>* Give with meals * Do not break, crush or chew tablets</td>
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<td><strong>Hypocalcemia</strong></td>
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<td>Calcium</td>
<td>Calcium replacement</td>
<td>Varies based on salt form</td>
<td>Varies based on salt form</td>
<td>Constipation, Bloating, Flatulence</td>
<td>* Ideal management is correction of hypophosphatemia * Not recommended in asymptomatic patients * Intravenous calcium should be given via central line only</td>
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<td><strong>Hyperuricemia</strong></td>
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<td>Sodium bicarbonate</td>
<td>Increases solubility of uric acid by alkalization of the urine</td>
<td>Initial 4 gm (48 mEq) PO followed by 1-2 gm (12-24 mEq) PO Q 4 hours with dose titrated to effect</td>
<td>84-840 mg (1-10 mEq)/kg/day PO in divided doses Q 4-8 hours with dose titrated to effect maximum daily dose: ~ 17 gm (200 mEq) in adults &lt;60 years of age and ~ 8 gm (100 mEq) in adults &gt;60 years</td>
<td>Metabolic alkalosis, Hypertension, Edema</td>
<td>* Urine pH goal is &gt; 7 * Use can lead to calcium-phosphate precipitation * Use with caution in patients with heart failure or renal failure * If placed in IV fluids, usually done as sodium acetate or sodium bicarbonate at 40-150 mEq/L so as not to exceed a total of 154 mEq sodium/L from all sources</td>
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<td>Acetazolamide</td>
<td>Carbonic anhydrase inhibitor that decreases bicarbonate reabsorption in the kidney which causes urinary alkalization as well as increases in renal excretion of sodium, potassium, bicarbonate and water</td>
<td>5 mg/kg/dose IV/Q 8-12 hours</td>
<td>5 mg/kg/dose IV/Q 8-12 hours</td>
<td>Metallic taste, Anorexia, Nausea, Vomiting, Diarrhea, Malaise, Muscle weakness, Rash</td>
<td>* Urine pH goal is &gt; 7 * Use as an alternative to sodium bicarbonate when fluid overload is a concern * Contraindicated in patients with systemic acidosis * Use with caution in patients with diabetes * Requires dose adjustment with renal dysfunction</td>
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<td>Allopurinol (Zyloprim®, Aloprim™, Lopurin®, Zurinol®)</td>
<td>Hypoxanthine analogue that decreases the formation of new uric acid by inhibiting xanthine oxidase</td>
<td>200-400 mg/m²/day IV or</td>
<td>200-300 mg/m²/day PO in single or divided dose</td>
<td>Rash, Pruritis, Nausea, Vomiting, Dyspepsia, Fever, Hypersensitivity syndrome, Eosinophilia, Interstitial nephritis, Xanthine nephropathy</td>
<td>* Does not affect existing levels of uric acid * Onset is 2-3 days with maximal effect seen in 7-14 days * Daily oral doses above 300 mg should be given in divided doses * Requires dose reductions in patients with renal dysfunction * Major drug interactions with mercaptopurine and azathioprine</td>
</tr>
<tr>
<td>Rasburicase (Elitek®)</td>
<td>Recombinant urate oxidase that catalyzes uric acid to allantoin</td>
<td>0.15-0.2 mg/kg/dose IV over 30 minutes daily for 1-5 days</td>
<td>0.15-0.2 mg/kg/dose IV over 30 minutes daily for 1-5 days</td>
<td>Nausea, Vomiting, Fever, Headache, Rash, Abdominal pain, Constipation, Diarrhea, Anaphylaxis, Bronchospasm, Hemolysis, Methemoglobinemia</td>
<td>* Contraindicated in G-6PD deficiency * Onset is within a few hours * No dose adjustments needed for renal or hepatic dysfunction * No known drug interactions * Keep blood samples on ice and process within 4 hours</td>
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References and Additional Information


Self-Assessment Questions

1. Which of the following is not a laboratory abnormality associated with tumor lysis syndrome?
   a. Hypercalcemia
   b. Hyperphosphatemia
   c. Hyperkalemia
   d. Hyperuricemia

2. The renal dysfunction associated with TLS can be due to all of the following EXCEPT
   a. Uric acid nephropathy
   b. Tumor invasion
   c. Hypovolemia
   d. Ischemia

3. Which of the following agents can be used to augment forced diuresis by hydration?
   a. Furosemide
   b. Hydrochlorothiazide
   c. Sodium bicarbonate
   d. Spironolactone

4. Which of the following is the most appropriate fluid choice to hydrate a patient receiving rasburicase to
   prevent the occurrence of TLS?
   a. D5NS with 50 mEq of sodium bicarbonate
   b. D51/2NS with 50 mEq of sodium bicarbonate
   c. D51/2NS
   d. LR

Answers:
1. a
2. d
3. a
4. c