Oncology Investigators Provide Perspectives on the Prevention and Management of Tumor Lysis Syndrome

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OVERVIEW OF ACTIVITY
Tumor lysis syndrome (TLS) is an oncologic emergency characterized by the rapid onset of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and/or acute renal failure. Despite the relatively rare incidence of TLS, the clinical landscape of this syndrome changed dramatically with the April 11, 2016 FDA approval of the Bcl-2 inhibitor venetoclax for relapsed/refractory chronic lymphocytic leukemia (CLL) harboring the del(17p) chromosomal abnormality. Given the availability of venetoclax and emerging evidence of its antitumor activity in non-del(17p) CLL and other cancer types, it is likely that concern over TLS will greatly increase in general oncology practice. To bridge the gap between research and patient care, this program uses one-on-one discussions with leading oncology and nephrology investigators to help overcome clinician uncertainties and alleviate current practice gaps surrounding the prevention and management of this potentially devastating complication of effective cancer treatment.

LEARNING OBJECTIVES
- Understand the pathophysiology of TLS, recognize its disease- and treatment-related risk factors and establish an evidence-based approach for the prevention and management of this oncologic emergency.
- Identify patients at increased risk for TLS or its complications (eg, those with increased baseline uric acid, the elderly, those with renal or cardiac dysfunction), and institute appropriate treatment modifications, including early intervention with rasburicase.
- Formulate an approach to manage TLS-associated metabolic abnormalities — hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and concomitant renal insufficiency — including recognition of when nephrology consultation is warranted.
- Appraise the risk-benefit profiles of chemoimmunotherapy treatments and targeted agents and regimens for CLL, and develop management strategies for the unique toxicities associated with recently approved therapeutics.
- Recognize the increased risk of TLS in patients with CLL treated with venetoclax, and implement approaches to ensure that appropriate administration protocols are followed to mitigate the risk of this potentially fatal toxicity.

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**FACULTY** — Dr Lahoti had no relevant conflicts of interest to disclose. The following faculty (and his spouse/partner) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Wierda — Consulting Agreement: Sanofi Genzyme; Contracted Research: AbbVie Inc, Acerta Pharma, Genentech BioOncology, Gilead Sciences Inc, GlaxoSmithKline, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma Inc, miRagen Therapeutics Inc, Novartis, Pharmacyclics LLC, an AbbVie Company, Sunesis Pharmaceuticals Inc.


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Tracks 1-27

**Track 1**  
*Case:* A 28-year-old man with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia starts induction hyper-CVAD and dasatinib.

**Track 2**  
Diagnostic criteria and identification of patients at risk for tumor lysis syndrome (TLS).

**Track 3**  
Clinical care of patients at high risk for TLS.

**Track 4**  
Allopurinol for hyperuricemia in patients at lower risk for TLS.

**Track 5**  
Rasburicase for patients at higher risk for TLS.

**Track 6**  
Correlation between bulk of disease and clinical course of TLS.

**Track 7**  
TLS-associated renal failure.

**Track 8**  
*Case:* A 60-year-old man with previously untreated Stage III trisomy 12 chronic lymphocytic leukemia (CLL) harboring an IGHV gene mutation receives FCR and prophylactic allopurinol.

**Track 9**  
Relationship between renal function and risk of TLS.

**Track 10**  
Management of anti-CD20 antibody-related infusion reactions.

**Track 11**  
Infrequency of TLS in solid tumors.

**Track 12**  
Gradual dose escalation with venetoclax to mitigate the risk of TLS.

**Track 13**  
TLS as an on-target effect of venetoclax in CLL.

**Track 14**  
Investigational strategies combining venetoclax with other agents in CLL.

**Track 15**  
Tolerability of venetoclax in CLL.

**Track 16**  
Complementary activity of venetoclax and ibrutinib.

**Track 17**  
*Case:* A 70-year-old patient with previously treated CLL and 17p deletion experiences disease progression and receives venetoclax.

**Track 18**  
Risk stratification for TLS in patients initiating treatment with venetoclax.

**Track 19**  
Creatinine clearance as a modifier of TLS risk.

**Track 20**  
Algorithm for patients at high risk for TLS who are initiating venetoclax treatment.

**Track 21**  
Approach for patients at medium risk for TLS who are initiating venetoclax treatment.

**Track 22**  
Use of venetoclax in lieu of ibrutinib in patients with atrial fibrillation who are receiving anticoagulation treatment.

**Track 23**  
Rates of ibrutinib discontinuation due to toxicity.

**Track 24**  
Restarting dose escalation of venetoclax after a treatment hold.

**Track 25**  
*Case:* A 72-year-old patient with previously treated CLL and a low creatinine clearance receives salvage venetoclax.

**Track 26**  
Potential for fixed-duration or endpoint-based treatment with venetoclax in CLL.

**Track 27**  
*Case:* A 62-year-old patient with CLL and a low risk of TLS initiates dose-escalation treatment with venetoclax.

Tracks 1-36

**Track 1**  
Incidence of TLS in patients receiving CAR T-cell therapy.

**Track 2**  
Pathophysiology of TLS.

**Track 3**  
Monitoring renal function in patients at risk for TLS.

**Track 4**  
*Case:* A 46-year-old man with metastatic melanoma and chronic renal disease experiences TLS after initiating nanoparticle albumin-bound (nab) paclitaxel.
Interview with Dr Lahoti (continued)

Track 5  Renal-associated toxicities in patients receiving immune checkpoint inhibitors

Track 6  Differing mechanisms of action of allopurinol and rasburicase

Track 7  Dosing, administration and tolerability of rasburicase

Track 8  Clinical consequences of hyperkalemia

Track 9  Supportive measures for patients experiencing hyperkalemia

Video Program

View the corresponding video interviews with (from left) Drs Wierda and Lahoti by Dr Love at www.ResearchToPractice.com/TumorLysis17/Video

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Submit them to us via Facebook or Twitter and we will do our best to get them answered for you

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SELECT PUBLICATIONS

A phase II study of venetoclax and ibrutinib in patients with chronic lymphocytic leukemia (CLL). NCT02756897


Standard chemoimmunotherapy (FCR/BR) versus rituximab + venetoclax (RVe) versus obinutuzumab (GA101) + venetoclax (GVe) versus obinutuzumab + ibrutinib + venetoclax (GIVe) in fit patients with previously untreated chronic lymphocytic leukemia (CLL) without del(17p) or TP53 mutation (GAIA). NCT02950051


Study of ibrutinib combined with venetoclax in subjects with mantle cell lymphoma (SYMPATICO). NCT03112174


1. TLS is characterized by the rapid onset of ________________.
   a. Hyperkalemia
   b. Hyperuricemia
   c. Hyperphosphatemia
   d. Hypocalcemia
   e. All of the above
   f. Both a and c
   g. Both b and d

2. Use of rasburicase is contraindicated in patients with ________________.
   a. 17p deletion
   b. G6PD (glucose-6-phosphate dehydrogenase) deficiency
   c. Trisomy 12

3. Venetoclax is currently FDA approved for the treatment of ________________ in patients who have received at least 1 prior therapy.
   a. CLL with 17p deletion
   b. CLL without 17p deletion
   c. Both a and b
   d. Neither a nor b

4. Which of the following is the mechanism of action of venetoclax?
   a. Bcl-2 inhibitor
   b. CAR T-cell therapy
   c. Immune checkpoint inhibitor

5. Venetoclax is dosed and administered in which of the following fashions?
   a. 20 mg once daily
   b. 400 mg once daily
   c. Initiated at 20 mg and gradually escalated to the target dose of 400 mg once daily

6. Hospitalization for the purpose of inpatient monitoring for TLS is required for all patients initiating therapy with venetoclax.
   a. True
   b. False

7. Which of the following is the most common toxicity other than TLS for which venetoclax is dose reduced?
   a. Diarrhea
   b. Fatigue
   c. Neutropenia

8. Patients with severe TLS can experience acute renal failure, although this issue is typically reversible.
   a. True
   b. False

9. Which side effect is of greatest concern for patients with acute leukemias receiving CAR T-cell therapy?
   a. Cytokine release syndrome
   b. Renal failure
   c. TLS

10. A meta-analysis published by Feng and colleagues evaluating the efficacy and cost of single-dose rasburicase versus the FDA-approved daily dosing of rasburicase for 5 days in the prevention and treatment of TLS demonstrated response rates with the single-dose approach to be ________________ to those with daily dosing for the prophylaxis of high-risk TLS.
    a. Inferior
    b. Noninferior/equivalent
    c. Superior
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**PART 1 — Please tell us about your experience with this educational activity**

How would you characterize your level of knowledge on the following topics?

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<th>AFTER</th>
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<td>4 = Excellent</td>
<td>3 = Good</td>
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- Strategies to effectively mitigate TLS in patients initiating venetoclax treatment (ie, dose ramping, prophylaxis, monitoring, et cetera)
- Results of a meta-analysis evaluating single-dose rasburicase versus the FDA-approved daily dosing of rasburicase for 5 days in the prevention and treatment of TLS
- Investigational strategies and ongoing trials evaluating venetoclax-based regimens for CLL
- Risk-benefit ratio for patients with aggressive lymphomas treated with CAR T-cell therapy

**Practice Setting:**
- Academic center/medical school
- Community cancer center/hospital
- Group practice
- Solo practice
- Government (eg, VA)
- Other (please specify) ..........................................................

Approximately how many of your patients develop TLS per year? ............... patients

Was the activity evidence based, fair, balanced and free from commercial bias?
- Yes
- No

If no, please explain: .............................................................................

Please identify how you will change your practice as a result of completing this activity (select all that apply).
- This activity validated my current practice
- Create/revise protocols, policies and/or procedures
- Change the management and/or treatment of my patients
- Other (please explain): ..........................................................................

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-------------------------------------------------------------------------

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- Yes
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As a result of this activity, I will be able to:
- Understand the pathophysiology of TLS, recognize its disease- and treatment-related risk factors and establish an evidence-based approach for the prevention and management of this oncologic emergency. ........................................ 4 3 2 1 N/M N/A
- Identify patients at increased risk for TLS or its complications (eg, those with increased baseline uric acid, the elderly, those with renal or cardiac dysfunction), and institute appropriate treatment modifications, including early intervention with rasburicase. ....... 4 3 2 1 N/M N/A
- Formulate an approach to manage TLS-associated metabolic abnormalities — hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and concomitant renal insufficiency — including recognition of when nephrology consultation is warranted. .............................................................. 4 3 2 1 N/M N/A
EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

• Appraise the risk-benefit profiles of chemoimmunotherapy treatments and targeted agents and regimens for CLL, and develop management strategies for the unique toxicities associated with recently approved therapeutics. 4 3 2 1 N/M N/A
• Recognize the increased risk of TLS in patients with CLL treated with venetoclax, and implement approaches to ensure that appropriate administration protocols are followed to mitigate the risk of this potentially fatal toxicity. 4 3 2 1 N/M N/A

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<tr>
<td>William G Wierda, MD, PhD</td>
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<td>Amit Lahoti, MD</td>
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<td>Neil Love, MD</td>
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