



Tumor Lysis Syndrome

Shital Patel, Pharm.D.
Memorial Healthcare System

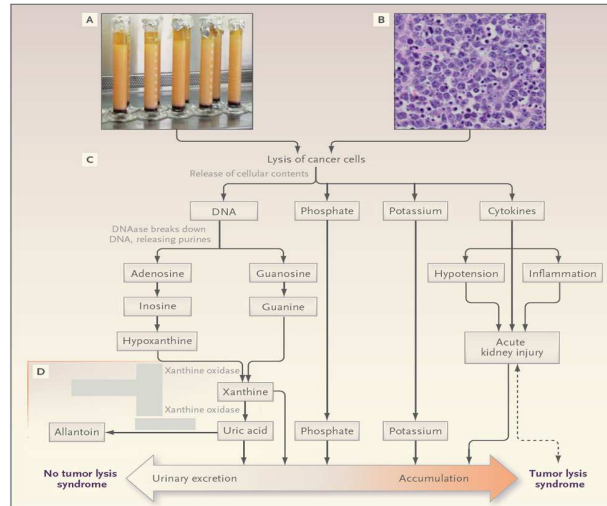


Tumor Lysis Syndrome (TLS)

- Oncologic emergency
- Tumor cell contents released into bloodstream
 - Overwhelm homeostatic mechanisms
- Electrolyte/metabolic disturbances
 - Hyperuricemia
 - Hyperkalemia
 - Hyperphosphatemia
 - Hypocalcemia

Howard SC, et al. *N Engl J Med*. 2011.

Pathophysiology



Howard SC, et al. *N Engl J Med.* 2011.

Complications

- Hyperkalemia
 - Dysrhythmias
- Hyperphosphatemia
 - N/V/D, Lethargy, Seizures
 - 2° Hypocalcemia
 - Tetany
 - Dysrhythmias
 - Seizures
 - Calcium/phosphate crystallization

Howard SC, et al. *N Engl J Med.* 2011.

Complications

- Hyperuricemia
 - Intrarenal crystallization
- Cytokine release
 - Systemic Inflammatory Response Syndrome (SIRS)
- Acute Kidney Injury

Howard SC, et al. *N Engl J Med.* 2011.

Defining TLS

Metabolic Abnormality	Laboratory TLS (Adult values)	Clinical TLS
Hyperuricemia	Uric Acid >8 mg/dl	N/A
Hyperphosphatemia	Phosphorus >4.5 mg/dl	N/A
Hyperkalemia	Potassium >6 mmol/l	Cardiac dysrhythmia or death attributed to hyperkalemia
Hypocalcemia	Corrected Calcium <7 mg/dl	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability, hypotension, or heart failure attributed to hypocalcemia
Acute kidney injury (AKI)	N/A	Increase in serum creatinine of 0.3 mg/dl (or single value > 1.5 x ULN of age specific normal range for population baseline), or oliguria (average urine output < 0.5 ml/kg/hr x6 hrs)

Howard SC, et al. *N Engl J Med.* 2011.

Risk Factors

- Cancer Mass
- Cell Lysis Potential
- Pre-existing Nephropathy
- Acidic Urine
- Hypotension
- Exposure to nephrotoxins

Howard SC, et al. *N Engl J Med.* 2011.
Cairo MS, et al. *Br J Haematol* 2010.

Risk Classification

Table 1. TLS Risk Classification^{5,6}

<p>High TLS Risk Hyperuricemia of malignancy (plasma uric acid >7.5 mg/dL) <i>or</i> Very aggressive lymphoma/leukemia (per REAL/WHO criteria) <i>or</i> Acute myeloid leukemia <i>or</i> Chronic myeloid leukemia in blast crisis <i>or</i> High-grade MDS with >10% bone marrow involvement</p> <p>Intermediate TLS Risk Aggressive lymphoma/leukemia (per REAL/WHO criteria) <i>plus</i> 1 or more of the following criteria: LDH >2 × ULN stage III-IV disease stage I-II disease with at least 1 lymph node/tumor mass >5 cm in diameter</p> <p>Low TLS Risk All other hematologic malignancies and solid malignancies</p> <p>LDH = lactate dehydrogenase; MDS = myelodysplastic syndrome; REAL = revised European-American lymphoma; TLS = tumor lysis syndrome; ULN = upper limit of normal; WHO = World Health Organization.</p>

Vines AN, et al. *Ann Pharmacother.* 2010.



Prevention of TLS

- Aggressive Hydration
- Diuretics
- Urine alkalinization
- Allopurinol
- Rasburicase

Howard SC, et al. *N Engl J Med.* 2011.



Aggressive Hydration/Diuretics

- 2-3 L/m²
- Loop diuretic

- Urine output: 80-100 mL/m²/hr

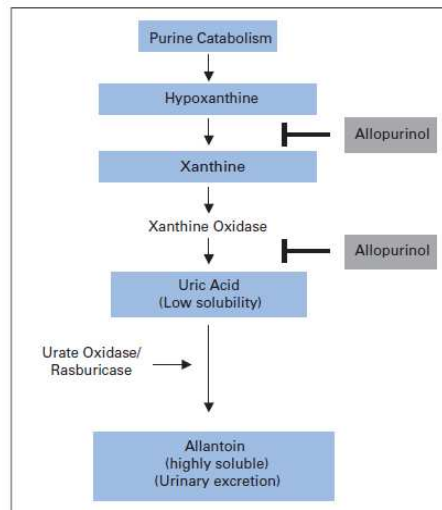
Coiffier B, et al. *J Clin Oncol.* 2008.

Urine Alkalinization

- Increases uric acid solubility
- Decreases calcium phosphate solubility
- Generally should be avoided
- Stop if hyperphosphatemia develops
- Unclear Benefit for AKI Prevention

Coiffier B, et al. *J Clin Oncol.* 2008.

Allopurinol vs. Rasburicase Mechanism of Action



Coiffier B, et al. *J Clin Oncol.* 2008.



Allopurinol

- Hypoxanthine Analog
 - Inhibits Xanthine Oxidase
- Prevents uric acid formation
 - Does not get rid of already existing uric acid
 - Existing uric acid levels take about 24-48 hrs to decrease
- Xanthine accumulation
 - Levels not routinely checked
 - Xanthine nephropathy

Howard SC, et al. *N Engl J Med.* 2011.



Allopurinol

- PO and IV
- Cheap
- Start 1-2 days before chemotherapy
- Dosing
 - PO: 600-800 mg/day DVD 2-3 doses
 - Max 800 mg/day
 - IV: 200-400 mg/m²/day DVD 1-3 doses
 - Max 600 mg/day
- Dose Adjustment in Renal Impairment
 - Clcr 10-20 mL/minute: 200 mg/day
 - Clcr 3-10 mL/minute: ≤100 mg/day
 - Clcr <3 mL/minute: 100 mg/dose at extended intervals

Howard SC, et al. *N Engl J Med.* 2011.

Allopurinol Package Insert



Rasburicase (Elitek®)

- Recombinant urate oxidase enzyme
- Catalyzes uric acid into allantoin (highly soluble)
 - Decreases existing levels of uric acid within 4 hours
- Uric acid blood sample
 - Keep on ice

Howard SC, et al. *N Engl J Med.* 2011.



Rasburicase (Elitek®)

- IV infusion only (NS 50 ml over 30 minutes)
- Expensive, Vial size: 1.5 mg, 7.5 mg
- Start before chemotherapy
- Contraindication: G6PD deficiency
- Dose: 0.2 mg/kg/day x5 days
- Other dosing
 - 0.05-0.2 mg/kg/day x1-7 days
 - Off label Single Dosing - Reasonable
 - 0.15 mg/kg x 1 dose only
 - 0.05 mg/kg x1 dose only
 - 3 mg x1 dose only
 - **6 mg x1 dose only**
 - 7.5 mg x1 dose only

Howard SC, et al. *N Engl J Med.* 2011.

Vines AN, et al. *Ann Pharmacother.* 2010.

Elitek® Package Insert.

Rasburicase vs. Allopurinol

Outcome (N= 280)	Rasburicase (n= 92)	Rasburicase + Allopurinol (n= 92)	Allopurinol (n= 91)
Uric acid response rate	87%*	78%*	66%
Median time to plasma uric acid control	4 hours*	4 hours*	27 hours
Laboratory TLS	21%*	27%	41%
Clinical TLS	3%	3%	4%

*Statistically significant

Cortes J, et al. *J Clin Oncol.* 2010.

Rasburicase Off-Label Dosing

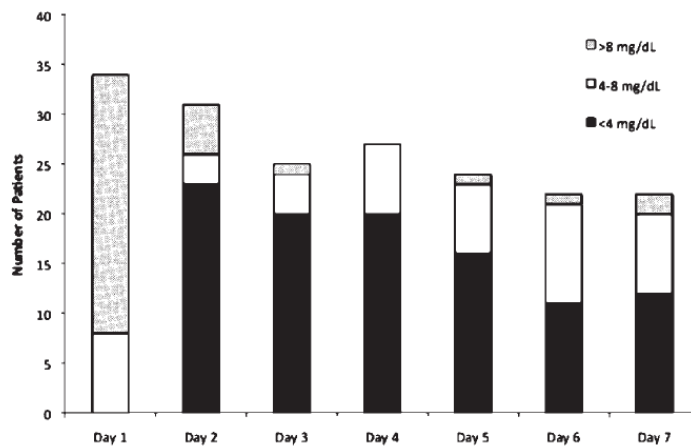
Table 2. Rasburicase Off-Label Dose Studies

Reference	Patients (n)	Study Design	Type of Malignancy Included	Dose/Duration	Uric Acid Response	SCr Response
Hutcherson (2006) ⁷	11	Retrospective	AML, multiple myeloma, Burkitt's lymphoma, MDS, CLL, adenocarcinoma, lung cancer	6 mg × 1 (0.045–0.1 mg/kg)	Decreased to <8 mg/dL in 10 pts. within 12–18 h	NR
McDonnell (2006) ⁸	11	Retrospective	NHL, AML, CMML, ALL, MDS, Burkitt's lymphoma, CML	6 mg × 1 (0.023–0.136 mg/kg)	Median decrease of 83% (11.7–2 mg/dL) in 10 pts. within 24 h	NR
Trifilo (2006) ⁹	43	Retrospective	Plasma cell dyscrasias, NHL, AML, CLL, MDS	3 mg × 1 (average 0.035 mg/kg)	Median decrease of 43% in 24 h; 37 pts. received 1 dose	Decreased by >10% in 18 pts. at 24 h
Reeves (2008) ¹⁰	17 vs 23	Prospective	NHL, leukemia, solid tumors	7.5 mg × 1 vs 0.15 mg/kg × 1	Mean decrease over 12 h of 82% vs 91% (p = 0.04)	Decrease over 96 h of 10.5% vs 20.2% (p = 0.16)
Hummel (2008) ¹¹	50	Prospective	ALL, AML, CLL, MDS, NHL, multiple myeloma, solid tumors	Physician discretion; median total dose 0.049 mg/kg (1–8 doses)	Decreased by 83% overall; 25 pts. received 1 dose (1.5–9 mg)	Normalized within 7 days in 28 of 42 pts. with elevated SCr at baseline
Campara (2009) ¹²	21	Retrospective	Acute/chronic leukemias, NHL, multiple myeloma, plasma cell leukemia, myelofibrosis	0.15 mg/kg average × 1 (0.11–0.24 mg/kg)	Decreased by 89.7 ± 9% for all pts. within 24 h (p < 0.001)	Decreased by 62% within 72 h in 13 of 21 pts. (p = 0.14)
Knoebel (2010) ¹³	48	Retrospective	Leukemia/lymphoma, WBC count ≥50 × 10 ⁹ /L, LDH >2 ULN, SCr ≥1.5 mg/dL	0.05 mg/kg × 1	Maintained <8 mg/dL in 40 pts. (p < 0.001)	NR

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CMML = chronic myelomonocytic leukemia; LDH = lactate dehydrogenase; MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma; NR = not reported; SCr = serum creatinine; ULN = upper limit of normal; WBC = white blood cells.

Vines AN, et al. *Ann Pharmacother.* 2010.

Rasburicase Single 6 mg Dosing



Vines AN, et al. *Ann Pharmacother.* 2010.

Place in Therapy

- Low risk
 - ±Allopurinol
- Intermediate risk
 - Allopurinol
 - Low-dose Rasburicase - Controversial
- High risk
 - Rasburicase

Cortes J, et al. *J Clin Oncol.* 2010.



Treatment of TLS

- Electrolyte abnormalities
 - Hyperkalemia
 - Hyperphosphatemia
 - Hypocalcemia

- Hyperuricemia
 - Allopurinol
 - Rasburicase

Cortes J, et al. *J Clin Oncol*. 2010.



Monitoring

- I/Os
- Weight
- BMP q6-12h
- Uric Acid

Cortes J, et al. *J Clin Oncol*. 2010.



Other Considerations in TLS

- Low intensity chemotherapy regimens
- Delay of chemotherapy

Howard SC, et al. *N Engl J Med.* 2011.



Self-Assessment Question 1

Which of the following is not laboratory abnormality seen in tumor lysis syndrome?

- a) Hyperkalemia
- b) Hyperphosphatemia
- c) Hypercalcemia
- d) Hyperuricemia



Self-Assessment Question 2

Which of the following is true?

- a) Allopurinol decreases existing levels of uric acid
- b) Rasburicase decreases existing levels of uric acid
- c) All patients at risk of tumor lysis syndrome should be receive treatment with allopurinol or rasburicase



Self-Assessment Question 3

Single-dose Rasburicase may be sufficient for prevention and treatment of tumor lysis syndrome.

- a) True
- b) False



Self-Assessment Question 4

On average, you expect rasburicase therapy to decrease uric acid levels within _____.

- a) 4-6 hours
- b) 24 hours
- c) 48 hours
- d) 7 days



Self-Assessment Question 5

Which of the following is a major contraindication for rasburicase use?

- a) Severe renal impairment
- b) Severe hepatic impairment
- c) Glucose-6-phosphatase dehydrogenase deficiency
- d) Severe leukocytosis (WBC >100)



References

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- Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. *Ann Pharmacother*. 2010; 44(10): 1529-1537.
- Allopurinol Package Insert.
- Elitek® Package Insert.