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Pharmacologic Management of Tumor Lysis Syndrome in Adults

Introduction

1. Tumor lysis syndrome (TLS) constitutes the most frequent oncologic emergency.
2. It is developed by lysis of tumor cells, during or within 7 days of chemotherapy.
3. The output of large amounts of potassium, phosphate, and nucleic acid, can result in characteristic electrolyte disturbances and cause the characteristic life-threatening arrhythmias (from electrolyte imbalances) and AKI (from hyperuricemia or hyperphosphatemia).
4. TLS can occur spontaneously in any tumor type with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic agents especially clinically aggressive and highly aggressive lymphomas (the Burkitt subtype) and T-cell acute lymphoblastic leukemia (ALL).
5. The increase in frequency and severity of TLS in hematologic cancers is associated with the emergence of effective targeted anticancer drugs.

Treatment of common electrolyte and lab abnormalities

Hyperkalemia

- **Happens in initial stages, 12-24 hours post chemotherapy**
- The most dangerous electrolyte abnormality and us**ually requires urgent and aggressive treatment as it can quickly develop into an arrhythmia**
- Standardized treatment consists of short infusion of calcium gluconate or chloride with continuous cardiac monitoring, IV infusion of insulin and glucose**, and** nebulized **beta-2 agonist (albuterol) +/- loop diuretic to promote excretion of potassium and calcium gluconate; start dialysis in refractory cases**

Hypocalcemia

- **Secondary to hyperphosphatemia caused by the release from lysed cells**
- **Can lead to fatal cardiac arrhythmia, tetany, and seizures**
- **Treat symptomatic hypocalcemia with lowest dose of IV calcium gluconate** or chloride **to relief symptoms, or by correcting serum phosphorus levels**; **Reserve** IV calcium replacement **for patients with EKG changes, tetany, and convulsions**

Hyperuricemia

- **Develops 48-72 hours post chemotherapy**
- **Influx of nucleic acids from lysed cells is released into the blood and converted to uric acid by xanthine oxidase. Renal failure happens due to an increase of uric acid passage and secretions by the renal tubule normally recycled by purine salvage pathways.**
    - **Urine alkalinization use is controversial but may be considered in cases of no rasburicase and severe hyperuricemia**

Hyperphosphatemia

- **Typically develops 24-48 hours post chemo when level exceeds renal excretion capacity**
- **Can lead to hypocalcemia**
- **To reduce the risk of hyperkalemia and hyperphosphatemia, continuous modes of renal replacement function are preferred over intermittent hemodialysis**

IV Hydration

- Avoid calcium and potassium containing fluids due to the risk of hyperkalemia and hyperphosphatemia with calcium phosphate precipitation from tumor breakdown[2]

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Hypouricemic Agents

	Allopurinol	Rasburicase	Febuxostat
Dose	Oral: 300 mg/m^2/day or 10 mg/kg/day in 3 divided doses, q8h (max 800 mg/day) IV: 200-400 mg/m^2/day IV as a single dose or in 2-3 divided doses (max 600 mg/day)	Different dosing strategies based on baseline uric acid and risk level Comes in 1.5 or 7.5 mg vials; round the dose to the closest number of full vials to prevent waste (a flat dose of 3 mg is commonly used in adults) Manufacturer's labeling: 0.2 mg/kg IV over 30 min once daily for up to 5 days	Oral: 60 mg/day Doses of up to 120 mg/day PO have been studied in clinical trials
Administration	Hydrate to yield a daily output of at least 2L in adults and neutral or slightly alkaline urine Whenever possible, start treatment 1-2 days before chemo induction and continue up to 3-7 d after chemo until lab normalization	Infuse over 30 min; do not administer as an IV bolus Infuse through a separate line; if not possible, flush line with at least 15 mL saline prior to and following infusion	Administer with or without meals or antacids
MOA	Structural analog of hypoxanthine. Inhibits xanthine oxidase, the enzyme responsible for conversion of hypoxanthine to xanthine and xanthine to uric acid	Recombinant form of urate-oxidase, the enzyme that catalyzes uric acid to allantoin (the inactive and more soluble metabolite)	Non-purine xanthine oxidase inhibitor
Adverse Effects	Acute gout attacks, hepatotoxicity, delayed hypersensitivity reactions	Moderate and common ADRs: antibody formation, constipation, edema, elevated hepatic enzymes, hyperbilirubinemia, hyperphosphatemia, hypophosphatemia, oral ulceration, peripheral edema	Moderate and common (>10%) ADRs: gout Severe and infrequent ADRs: atrial fibrillation, AV block
Drug Interactions and warnings	Major DDIs: aluminum hydroxide, azathioprine, capecitabine, didanosine, mercaptopurine, pegloticase, warfarin Avoid use in patients with the HLA-B*58:01 allele (particularly in certain Asian populations)	Major DDIs:, epinephrine, bupivacaine, lidocaine, penicillin G, prilocaine, ropivacaine, tetracaine Contraindicated in patients with G6PD	Fewer drug-drug interactions with febuxostat than with allopurinol Major DDIs: azathioprine, mercaptopurine Boxed Warning: risk of cardiovascular death
Comments	Works by decreasing uric acid formation. Does not acutely reduce uric acid levels, hence not the drug of choice in established TLS. Reduce dose by 50% in renal impairment due to potential for accumulation Use for the prevention* of hyperuricemia in patients at intermediate risk for TLS and without preexisting hyperuricemia	Drug of choice in established TLS; degrades preexisting uric acid and can normalize serum uric acid within 4 h in adults Dose adjustment not needed in patients with renal impairment Does not lead to xanthine accumulation Substantially declines the need for dialysis during induction therapy for high-risk hematologic malignancies Use in patients with preexisting hyperuricemia (uric acid≥7.5 mg/dL), high risk disease, or with intermediate-risk disease unresponsive to allopurinol	Shown similar efficacy at preventing TLS compared to allopurinol in intermediate-high risk groups[7] No dosage adjustment necessary for patients with mild-moderate renal impairment Good option for patients who cannot tolerate allopurinol and when rasburicase is not available or is contraindicated

* Use of prophylactic measures is indicated for patients without Cairo-Bishop definition of established TLS (Uric acid ≥8mg/dL, potassium ≥6mEq/L, phosphorus ≥6.5 mg/dL for children or ≥4.5 mg/dL for adults, calcium ≤7 mg/dL)

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Goldman, 2001	Multicenter RCT (n=52)	Pediatric patients with leukemia or lymphoma and at high risk for TLS received allopurinol (300 mg/m^2 or 10 mg/kg PO q8h) vs rasburicase (0.2 mg/kg IV daily) for 5-7 days	mean uric acid AUC(0-96) was 128 +/- 70 mg/dL.hour for the rasburicase group vs 329 +/- 129 mg/dL.hour for the allopurinol group (P <.0001) 86% vs 12% reduction (P <.0001) in initial plasma uric acid levels in the rasburicase vs allopurinol group shown 4 h post 1st dose **The study demonstrated more rapid control and lower levels of plasma uric acid in the rasburicase group**
Cortes, 2010	RCT (n=275)	Rasburicase (0.20 mg/kg/d IV days 1-5) vs rasburicase + allopurinol (rasburicase 0.20 mg/kg/d 1-3 followed by PO allopurinol 300 mg/d 3-5) vs allopurinol (300 mg/d PO d 1-5)	sUA response rate was significantly greater for rasburicase than for allopurinol (P=.001) in the overall study population, those at high risk for TLS (89% vs. 68%; P=0.012), and in patients with baseline hyperuricemia (90% vs. 53%; P=0.15) Time to sUA control in hyperuricemic patients was 4 h for rasburicase, 4 h for rasburicase + allopurinol, and 27 h for allopurinol Rasburicase was well tolerated and provided more rapid uric acid control than allopurinol alone
Vadhan-Raj, 2012	RCT (n=82)	Single dose rasburicase (0.15 mg/kg) followed by as needed dosing (max five doses) vs daily dosing for 5 days in adults	UA normalization achieved in 99% of patients within 4 h of the first dose and 84% reached undetectable levels(<0.7mg/dl) 98% in the daily-dose and 85% in the single-dose group showed sustained UA response Single-dose rasburicase was effective in most patients; only a subset of high-risk patients required a second dose
Bellos, 2019	Meta-analysis (n=658)	Febuxostat (10-120 mg/d) vs allopurinol (100-600 mg/d) in TLS prevention across six studies	Febuxostat achieved a similar response rate as allopurinol (OR: 1.39, 95% CI: [0.55, 3.51]) Similiar serum uric acid levels resulted between the two groups at day 2 (mean difference (MD): -0.21 mg/dL, 95% CI: [-1.30, 0.88]) and day 7 (MD: -0.43 mg/dL, 95% CI: [-1.38, 0.51]) of treatment Elevated LFTs was the most common ADR in both groups
Feng, 2013	Meta-analysis (n=269)	Ten studies evaluated the response rate and plasma UA level reduction of single dose rasburicase (from 0.05 mg/kg to 0.20 mg/kg) vs daily dosing rasburicase (0.2 mg/kg)	Single-dose rasburicase response rate was not significantly different than daily dose rasburicase (88.15% vs 90.18%, P=0.542) Single-dose rasburicase was significantly stronger than that of allopurinol given at 300 mg/day PO d1-5 (88.15% vs 66%, P<0.0005) Single-dose rasburicase has non-inferior clinical benefit and significant cost savings compared with the daily-dose regimen
Tamura, 2016	RCT (n=100)	Evaluated the non-inferiority of febuxostat to allopurinol based on AUC of serum UA for a 6-d treatment; Randomized intermediate-high risk patients to febuxostat (60 mg/day) or allopurinol (300 or 200 mg/day) taken 24 h before chemotherapy	The least squared mean difference of the AUC of sUA between the treatment groups was -33.61 mg h/dL, 95% CI -70.67 to 3.45 No differences in safety outcomes between the treatment groups The study demonstrated the non-inferiority of febuxostat to allopurinol

Conclusions

1. The best management of TLS is prevention and is usually based on the following risk stratification:
   - Low risk: observe and monitor S&S, hydration, +/- allopurinol
   - Intermediate risk: monitoring, hydration, and allopurinol (does not acutely reduce uric acid)
   - High risk: monitoring, aggressive IV hydration* and rasburicase (CI in G6PD; use allopurinol)
     *For severe-risk patients, use aggressive fluid hydration to achieve urine output of 80-100 mL/m^2 per hour (without CI for volume expansion) +/- loop diuretic (if no evidence of acute obstructive uropathy and/or hypovolemia)
2. Febuxostat is an alternative oral agent in patients who are at intermediate-high risk for TLS and cannot tolerate allopurinol and when rasburicase is not available or is contraindicated.
3. Urine alkalinization with sodium bicarbonate has fallen out of favor and is only indicated in patients with metabolic acidosis.
4. The emergent treatment of TLS involves vigorous hydration and careful monitoring of fluid balance, correcting electrolyte abnormalities, and possible renal replacement therapy.

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