Tumor Lysis Syndrome: An Endless Challenge in Onco-Nephrology

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Disclosure!

No potential Conflicts of interest to disclose!

Objectives

1. Define Tumor Lysis Syndrome (TLS) and its clinical importance in onco-nephrology.
2. Explain the biochemical and clinical mechanisms underlying TLS.
3. Identify patients at risk and understand stratification models.
4. Explore evidence-based prophylactic measures and updated management strategies

Tumor Lysis Syndrome

- **Cancer patients face increased risk of AKI:**

✓ Chemotherapy-induced vomiting.
✓ Nephrotoxic effects of anticancer drugs.
✓ Direct kidney damage from malignancy or obstruction.

Lupu¸ soru, M. Exp. Ther. Med. 2021,

Tumor Lysis Syndrome: Why It Matters

Overview of TLS:

- Rapid tumor cell lysis leads to metabolic disturbances.
- Potentially life-threatening complications like AKI, arrhythmias, and seizures.

Relevance in Cancer Patients:

- Common in hematologic malignancies (e.g., acute leukemia, Burkitt's lymphoma).
- Can occur spontaneously or after therapy.

In-hospital mortality of the cancer patient by up to 79% in cases of acute myeloid leukemia (AML) during induction therapy

Lupușoru, Exp. Ther. Med., 2021; Howard et al., N. Engl. J. Med., 2011,

Beyond Definitions: TLS in Focus 1993–2011

Cairo–Bishop Definition of Tumor Lysis Syndrome			
Laboratory TLS = modification of at least 2 parameters within 24 h	- Uric acid $\geq$ 8 mg/dL - Potassium $\geq$ 6 mg/dL - Phosphate $\geq$ 4.5 mg/dL	Or 25% increase	within 3 to 7 days after chemotherapy initiation
	- Calcium $\leq$ 7 mg/dL	Or 25% decrease	
Clinical TLS = laboratory TLS + 1 organ dysfunction or death	- Renal dysfunction (creatinine > 1.5 X normal values) - Cardiac involvement (arrhythmias) - Neurological involvement (seizures, tetany) - Death		

Cairo–Bishop Definition (2004): Expanded criteria to include spontaneous TLS and therapy-induced TLS
Howard and colleagues (2011): changes of the laboratory parameters must be simultaneous within 24 h
The same as the AKI definition (increase in Scr by 0.3 mg/dL or an increase to 1.5 times baseline or oliguria (UOP < 0.5 mL/kg/h for 6–12 h)

Cairo & Bishop, Br. J. Haematol., 2004; Howard et al., N. Engl. J. Med., 2011

TLS Epidemiology: Hidden Numbers, Hidden Dangers

Incidence:

- Laboratory TLS: 18.9% in leukemia/lymphoma patients.
- Clinical TLS: 5%.

21.4% and 5.2% in acute lymphoblastic leukemia (ALL), 14.7% and 3.4% in AML, and 19.6% and 6.1% in non-Hodgkin lymphoma

High-Risk Tumors: Burkitt's lymphoma, B-cell ALL, and AML with leukocytosis over 100,000/mm3

Low-Risk Tumors: Chronic leukemia, multiple myeloma.

Large tumors (over 10 cm) and those with local invasion or metastases also have a high risk of TLS.

Andronesi, Cancer Med. 2019 & Bahoush, J. Blood Disord. Transfus. 2015

Uncertainty!!

- **Cases of catastrophic TLS in low-risk tumors are also described:**
- A patient receiving cetuximab for metastatic colon cancer
- A patient with chronic leukemia who developed TLS during the first 24 h after starting imatinib.
- A patient with renal cell carcinoma treated with sunitinib.

- To the contrary, the TLS incidence may be significantly reduced in high-risk tumors (e.g., Burkitt's lymphoma) due to aggressive prophylactic therapy with hydration and Rasburicase.
- Tumor sensitivity to chemotherapy, tumor extension and metastases, and associated clinical conditions (CKD, hypovolemia, hypotension) also contribute to increased risk of TLS.

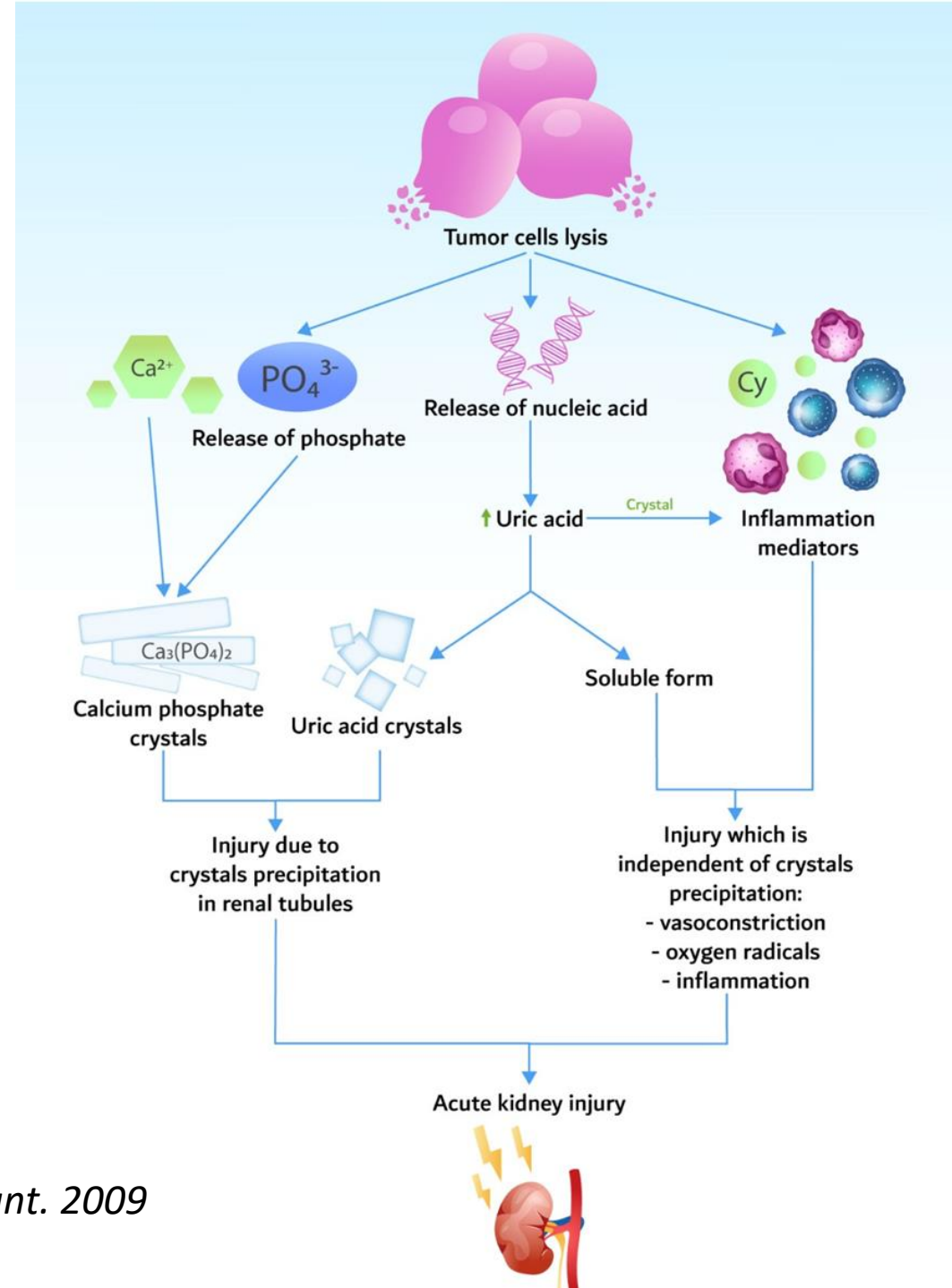
Michels, New Drugs 2010

TLS Pathogenesis:
Tumor Turnover Chaos

Tumor cell lysis releases:

- Potassium → Hyperkalemia.
- Phosphate → Hyperphosphatemia.
- Nucleic acids → Uric acid (hyperuricemia).
- Hypocalcemia → Neuromuscular and cardiac dysfunction.

- ***Cascade effects on kidneys, heart, and CNS.***



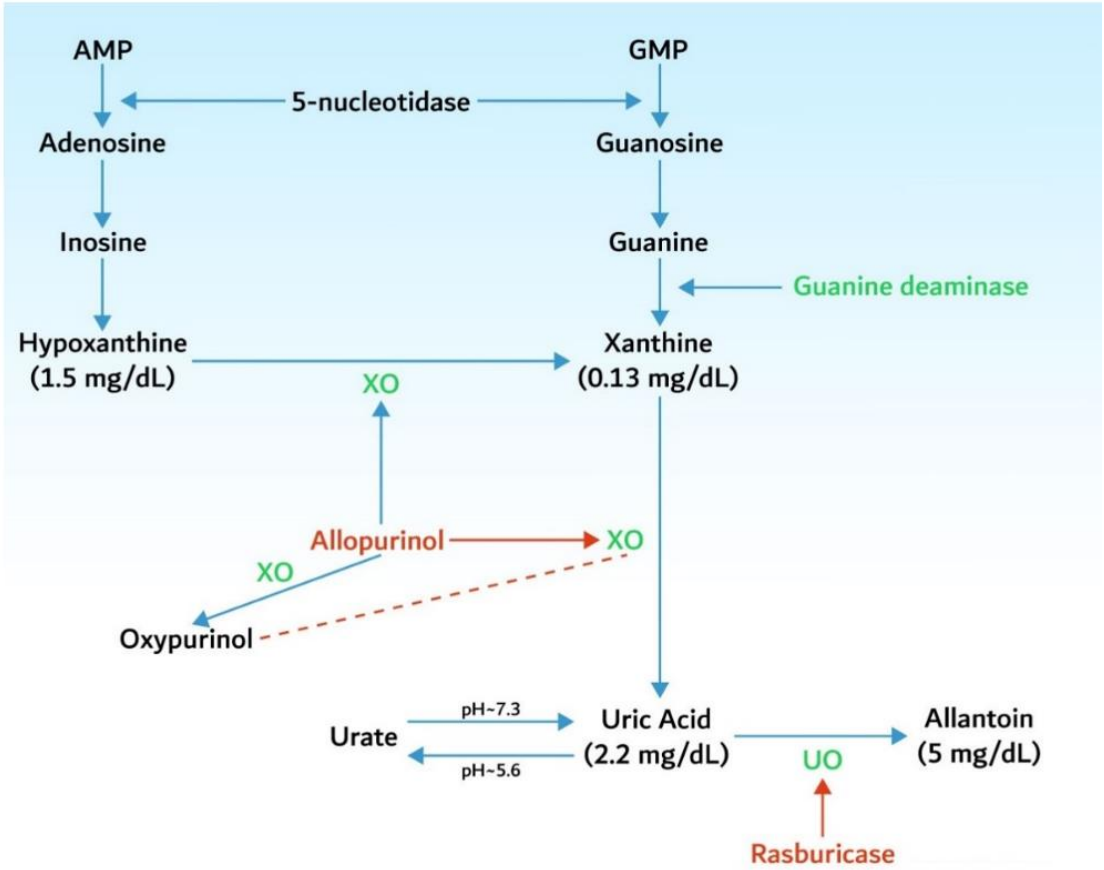
Shimada, Nephrol. Dial. Transplant. 2009

Inside Hyperuricemia

- Purine degradation → Uric acid.
- Humans lack urate oxidase (enzyme for UA breakdown).

Uric acid precipitates in renal tubules, causing:

- Tubular obstruction.
- Renal vasoconstriction and reduced autoregulation.



Shimada, Nephrol. Dial. Transplant. 2009

Hyperkalemia

- Tumor cell lysis releases large amounts of potassium into the circulation, and the uptake capacity by muscle and liver is exceeded.
- It is even more pronounced in the setting of chronic kidney disease (CKD) or pre-existing AKI.
- It can lead to muscle fatigue, paralysis, arrhythmia, and death.

Lupu¸ soru, M. Exp. Ther. Med. 2021,

Balancing the Calcium–Phosphate Scale

- **Phosphate binds calcium** → Precipitates in kidneys and soft tissues (nephrocalcinosis)

- Neuromuscular excitability with tetany, seizures

- Calcium phosphate can also precipitate in the conduction system of the heart, leading to conduction abnormalities and sometimes fatal arrhythmias.

- **Calcium-phosphate product** >70 mg^2/dL^2 → Dialysis indication.

Agnani, Int. J. Clin. Pract. 2005

Identification of Patients at Risk: for timely monitoring and prophylaxis intervention

- **High Risk (>5%):** Burkitt's lymphoma, ALL, AML.
- **Intermediate Risk (1–5%):** Solid tumors with large volumes
- **Low Risk (<1%):** Small indolent tumors (e.g., CLL)

Tumor Risk Factors Tumor's DNA	Patient-Related Risk Factors
Type of tumor	Male gender
Tumor volume (tumors > 10 cm)	Age > 65 years
Metastatic disease	Pretreatment serum creatinine > 1.4 mg/dL
Tumor growth rate (LDH > 2 times NV)	Renal obstruction
Level of leukocytosis (>25,000/mm^3)	Pretreatment serum uric acid > 7.5 mg/dL
Sensitivity to chemotherapy (germ cell tumors, small cell lung cancer, etc.)	Associated conditions (hypotension, hypovolemia, nephrotoxic drugs, CKD)

LDH—lactate dehydrogenase; CKD—chronic kidney disease; NV—normal value.

Coiffier J. Clin. Oncol. 2008

Risk Factors Related to Therapy

- Intrathecal chemotherapy, interferon, steroids, radiation therapy, and bortezomib–cyclophosphamide–dexamethasone combination (in patients with multiple myeloma), as well as fludarabine, rituximab, or ibrutinib for chronic lymphocytic leukemia (CLL), are often associated with TLS .

- Other substances and drugs (such as alcohol, caffeine, thiazide diuretics, acetylsalicylic acid, cisplatin, methyldopa, theophylline, pyrazinamide, diazoxide, ethambutol) that increase the level of serum uric acid can also increase the risk of TLS .

Jones Br. J. Haematol. 2015

Tumor Lysis Syndrome Management:

Prophylaxis

- Management should focus on identifying patients at risk to develop TLS and on prompt prophylaxis.

- The key to prophylaxis is to ***maintain an adequate urine output*** and to ***decrease the blood levels*** of uric acid, potassium, and phosphate.

- The ***monitoring*** of biological values are recommended to be done every 4 to 6 h after antitumor therapy initiation for patients at high risk; every 8 to 12 h for patients at intermediate risk; daily for patients at low risk.

➢ **In addition, it is recommended:**

- to avoid the nephrotoxic drugs (NSAIDs, contrast agents);
- to stop RAAS Blockade.

Lupușoru G, Biomedicines. 2022

Volume expansion: The urine output that should be obtained is over 100 mL/m2/h or a diuresis of 2.5 L/day for adults; over 4 mL/kg/h for children.

Diuretics: Thiazides are contraindicated because they increase the blood levels of uric acid.

Lupușoru G, Biomedicines. 2022

Urine alkalinization!!

Uric Acid Solubility: Alkalinization increases urate solubility but reduces uric acid crystal formation.
Calcium Phosphate Risk: Promotes calcium phosphate crystal precipitation.
Systemic Effects: Alkalosis can cause arrhythmias and tetany by increasing calcium binding.

Urine alkalinization is not recommended due to these risks.

Lupușoru G, Biomedicines. 2022

Hypocalcemia and Hyperkalemia

- Treatment is administered to alleviate the symptoms and not to normalize the calcemia.
- Hyperkalemia must be promptly treated because it can induce life threatening arrhythmias.
- When kalemia exceeds 7 mmol/L, dialysis is recommended.

Drugs That Increase the Release of the Potassium from the Cells
Beta-adrenergic blockers
Digoxin
Verapamil
Mannitol
Drugs that interfere with the renin–angiotensin–aldosterone system
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
NSAIDs
Calcineurin inhibitors
Heparin
Potassium sparing diuretics
Trimethoprim
Drugs that contain potassium
G penicillin
Frozen blood products

Lupușoru G, Biomedicines. 2022

Allopurinol: Stopping Uric Acid in Its Tracks

- A purine analogue and is the isomer of hypoxanthine. It is metabolized by xanthine oxidase to oxypurinol (the active form of allopurinol), which is a competitive inhibitor of xanthine oxidase.

- Oxypurinol has a half time of 24 h

- Oxypurinol decreases the production of uric acid from xanthine, but it has no effect on the uric acid that has been already synthetized. This leads to a weak response to treatment in patients with TLS and severe hyperuricemia. Moreover, in this case, the serum concentration of hypoxanthine and xanthine increases after allopurinol and xanthine can precipitate into the renal tubules, leading to AKI.

Bellinghieri Contrib. Nephrol. 2005,

Allopurinol

- Doses: 200–400 mg/m2/day, divided in 1 to 3 doses, to maximum 800 mg/day;

- ***In chronic kidney disease, the dose is adjusted according to (eGFR):***
  20–50 mL/min/1.73 m2: 200–300 mg/day;
  10–20 mL/min/1.73 m2: 100–200 mg/day;
  <10 mL/min/1.73 m2: 100 mg/day or every 2 days.

- Prophylactic therapy must begin at least 24 h prior to chemotherapy initiation and must be continued for at least 7 days.

Cairo *Br. J. Haematol*. **2010**

Allopurinol: drug interactions and Side effect

- **Azathioprine** Reduce the dose by 65–75%.
- Thiazides, cyclophosphamide, cyclosporine, ampicillin, and amoxicillin.
- Side effects are rare but may be life-threatening: from **Steven–Johnson syndrome , DRESS syndrome and Idiosyncratic reactions.**
- *As a prophylactic treatment and not in established TLS, where it can be used only if the patient is allergic to rasburicase or has glucose-6-phosphate dehydrogenase (G6PD) deficiency.*

Hung Proc. Natl. Acad. Sci. USA 2005

Rasburicase: Prevention and treatment of TLS

- Rasburicase is a recombinant variant of UO, derived from Aspergillus flavus. It was approved by FDA for pediatric patients with hematological malignancies undergoing chemotherapy in 2002 and for adults at risk for developing TLS in 2009.

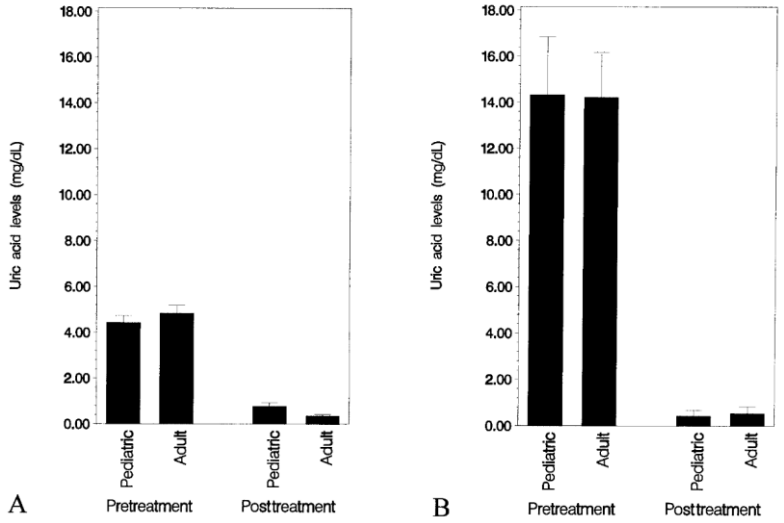
- Rasburicase is very well tolerated with only few side effects, has less drug interactions compared to allopurinol, and has a rapid effect (it lowers uric acid level in 4 h).

Malaguarnera Expert Opin. Pharmacother. 2009

Rasburicase: Prevention and treatment of TLS

- It was tested in 1069 pt for its efficiency in treating hyperuricemia and showed lower uric acid level in 99% of children and 100% of adults. Renal replacement therapies were necessary in only 2.8% of cases .

Vachhani (2021) [68]	Prospective, randomized study	24 (adults)	RSB—two treatment arms: - 1.5 mg—day 1 (Arm A) - 3 mg day 1 (Arm B) ALLP 300 mg on days 1–6 to all pts	The efficacity of two lower, single doses of RSB in decreasing UA levels	- 83% pts in both arms achieved PUA < 7.5 mg/dL by 24 h after therapy. - 21% pts required additional doses of RSB. - 23/24 of pts achieved UA goals after 1–2 doses of RSB.



(A) without or (B) with hyperuricemia

Malaguarnera Expert Opin. Pharmacother. 2009

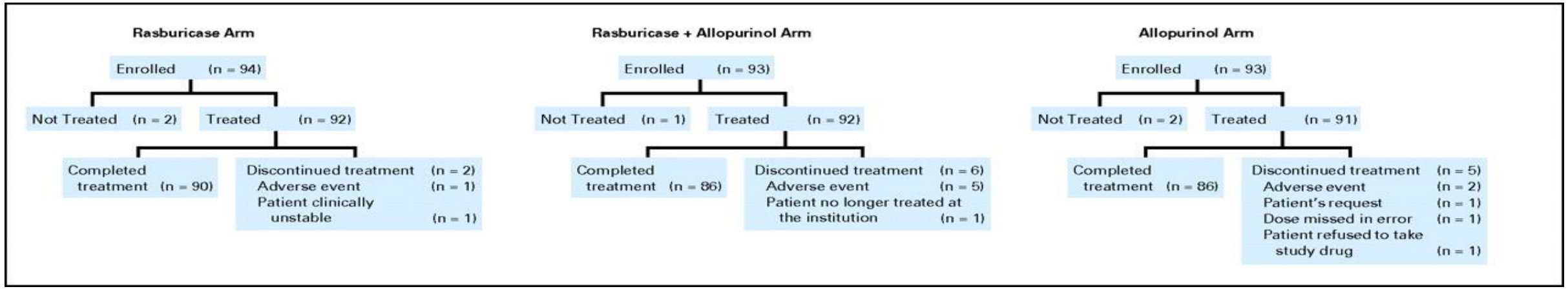
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

PARTIAL ACCESS | ORIGINAL REPORTS | August 16, 2010

Control of Plasma Uric Acid in Adults at Risk for Tumor Lysis Syndrome: Efficacy and Safety of Rasburicase Alone and Rasburicase Followed by Allopurinol Compared With Allopurinol Alone—Results of a Multicenter Phase III Study

Authors: Jorge Cortes, Joseph O. Moore, Richard T. Maziarz, Meir Wetzler, Michael Craig, Jeffrey Matous, Selina Luger, ... SHOW ALL ..., and Karen Seiter | AUTHORS INFO & AFFILIATIONS

Phase III study on patients at risk for TLS



Author (Year)	Modality	Sample Size	Treatment	Primary Outcome(s)	Results and Key Observations
Cortes (2010) [58]	Multicenter, randomized, comparative phase III study	275 (adults)	Three treatment arms: - RSB (n = 92) - RSB and ALLP (n = 92) - ALLP (n = 91)	Percentage of patients achieving PUA $\leq$ 7.5 mg/dL during days 3–7 of treatment	PUA response rate: ~87% with RSB, 78% with RSB and ALLP, 66% with ALLP. RSB was significantly better than ALLP in controlling PUA in terms of rapidity and efficacy.

Rasburicase: G6PD deficiency!!

- Rasburicase converts uric acid in allantoin, carbon dioxide and hydrogen peroxide. Accumulation of hydrogen peroxide in patients with leads to methemoglobin accumulation leading to hemolytic anemia.

- An initial dose of 0.05 mg/kg can be administered intravenously whenever testing is not possible. Regardless of this, these patients must be closely monitored for signs of hemolytic anemia.

- Rasburicase continues to be active ex vivo, thus leading to false decreased values of uric acid if the blood sample is not immediately delivered to the laboratory in ice recipients in order to be processed in no more than 4 h after blood collection.

- Rarely, it can induce rash, fever, headache, nausea, vomiting, or hepatic cytolysis and it is contraindicated in pregnancy, lactating women, or patients with G6PD deficiency.

Jones Br. J. Haematol. 2015

Rasburicase: British Committee of Standards in Hematology

- It is recommended to administer rasburicase as a prophylaxis to high-risk patients in a single dose of 3 mg to adults and 0.2 mg/kg to children.

- Rasburicase administration can be repeated daily for 5–7 days when necessary (lack of response or increase in the uric acid level).

Lupușoru G, Biomedicines. 2022

Treating Hyperphosphatemia

- Volume expansion with isotonic solutions, dietary phosphorus restrictions and the administration of oral phosphate chelating agents (e.g., sevelamer).

- Dialysis is indicated when the value of the calcium x phosphate product exceeds 70 mg2/dL2, despite the therapeutic and prophylactic measures.

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Established TLS Treatment

- ***Multidisciplinary approach*** and a careful monitoring of some key elements: regularly checking the patient because his general status may change from one hour to another, and monitoring diuresis, laboratory tests, and possible complications.

- It is recommended to maintain a urine output of at least 100 mL/m2/h for adults and 4 mL/kg/h for children. Urine alkalinization is not recommended ***(level 1C recommendation).***

- It is recommended to administer rasburicase and not xanthine oxidase inhibitors

Jones Br. J. Haematol. 2015

Established TLS Treatment

- As a therapy, the recommended dose of rasburicase is 0.2 mg/kg/day, and the treatment duration must be established according to clinical response, but no more than 3 to 7 days.

- Some studies still recommend a fixed, single dose of 6 mg, which was found to be as effective as the weight-adapted dose .

Browning Ann. Pharmacother. 2005

Established TLS Treatment: Renal

Replacement Therapy

- The necessity RRT decreased dramatically in the era of rasburicase.

- RRT is indicated when kidney dysfunction is aggravating despite therapeutic measures, when the patient develops **hypervolemia**, or when electrolyte disturbances are **refractory** to medical treatment.

- The options for RRT: Daily hemodialysis or continuous veno-venous hemofiltration.

- Combination of intermittent hemodialysis and continuous hemofiltration/hemodiafiltration for an efficient clearance of phosphate, which is time dependent.

- When necessary, RRT should be performed until urine output and electrolyte values return to normal.

Lupușoru G, Biomedicines. 2022

Tumor Lysis Syndrome : Future Perspectives

Prevention through Chemotherapy Modulation

Leuk Lymphoma. 2008 December ; 49(12): 2298–2307. doi:10.1080/10428190802517732.

Augmented and standard Berlin-Frankfurt-Münster chemotherapy for treatment of adult acute lymphoblastic leukemia

Julie E. Chang[1], Stephen C. Medlin[2], Brad S. Kahl[1], Walter L. Longo[1], Eliot C. Williams[1],

N Engl J Med. 2013 November 14; 369(20): 1915–1925. doi:10.1056/NEJMoa1308392.

Low-Intensity Therapy in Adults with Burkitt's Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Margaret Shovlin, R.N., Seth M.

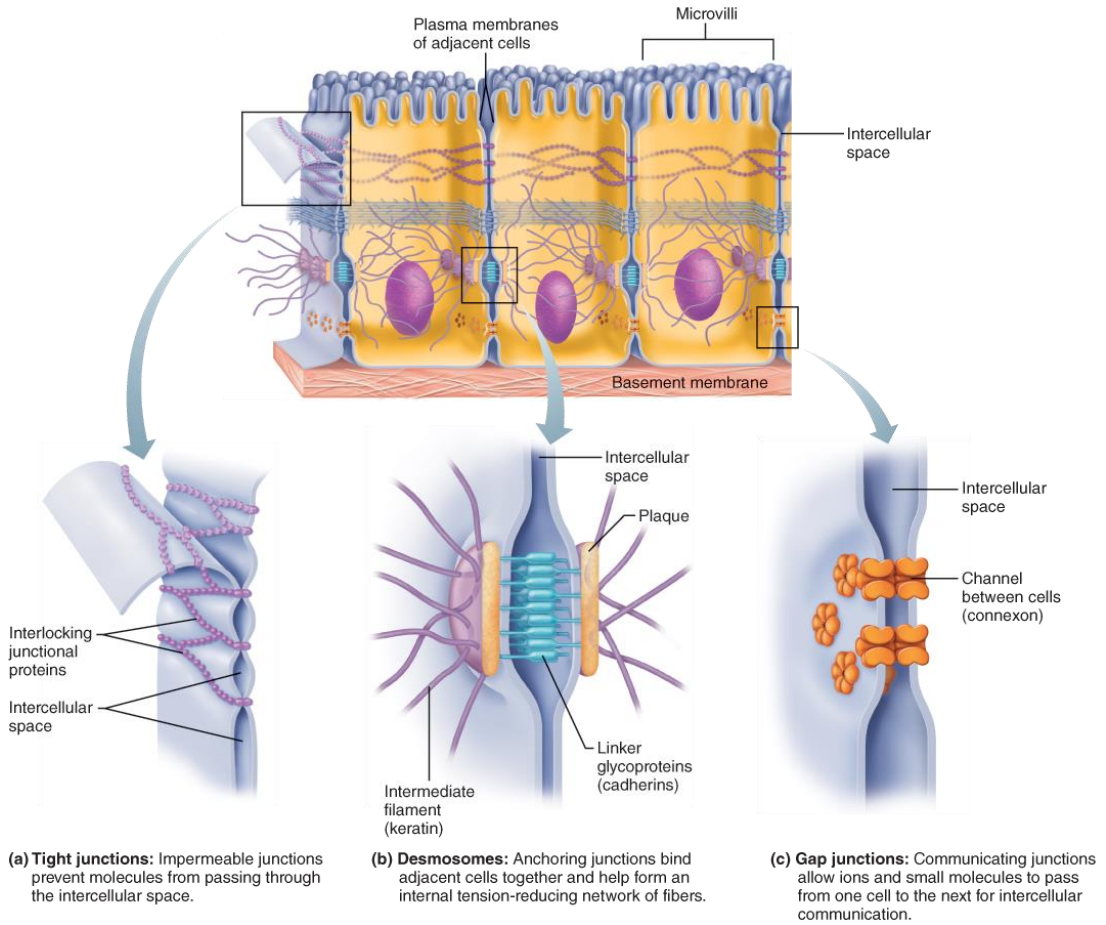
- Choosing less aggressive chemotherapy regimens to slowly reduce the tumor burden.
- Berlin–Frankfurt–Muenster group treated a child with ALL by initially administering prednisone for one week before initiating induction chemotherapy.
- For patients with Burkitt's lymphoma, there are regimens that include a first week of treatment with low doses of vincristine, prednisone, and cyclophosphamide, followed by full doses.

Galoian Mol. Clin. Oncol. 2015

Chemotherapy Modulation: Desmosome

- A series of studies have reported a correlation between reduced desmosome expression and the invasiveness of tumors,

- ***Transitional cell carcinoma of the bladder***
- ***Non-small cell lung cancer***.



Mirrakhimov Rare Tumors 2014

Enzyme Replacement Therapy: Oral recombinant urate oxidase (ALLN-346)

- Although the kidney is the major site of elimination for uric acid, the gut also plays an important role in urate metabolism. Oral recombinant urate oxidase (ALLN-346), which targets intestinal degradation of urate, was studied in mice deficient in uricase with severe hyperuricemia and crystalline obstructive nephropathy.

- ALLN-346 determined a significant reduction of hyperuricemia by 44% and the normalization of uricosuria.

Pierzynowska Front. Med. 2020

Enzyme Replacement Therapy: Pegloticase NCT04745910 phase-IV clinical trial

- Pegloticase is a third-line treatment that was authorized by the European Medicines Agency in 2016 for the treatment of severe, refractory gout. It is given as an intravenous infusion every two weeks.

- Pegloticase is a recombinant porcine uricase that is pegylated to increase its elimination half-life and to decrease the immunogenicity.

- Like rasburicase, it is contraindicated in patients with G6PD deficiency.

Take Home Points

- TLS is a **constellation of metabolic disorders** that occur to malignant cells lysis, related either to the treatment or to the increased rate of cells proliferation.

- TLS is an **onco-nephrology emergency**, with AKI being one of the most important predictors of short- and long-term mortality in these patients.

- According to TLS risk stratification, an **early, aggressive**, and **multidisciplinary approach** is mandatory to limit the occurrence of this condition and consequently of AKI.

- Nowadays, **new advances** in chemotherapy pose the risk of TLS developing even in patients with malignancies that were previously classified as having a low risk for this complication.


Thank you