Tumor Lysis Syndrome

Subjects: Oncology
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Tumor lysis syndrome (TLS) is a common cause of acute kidney injury in patients with malignancies, and it is a frequent condition for which the nephrologist is consulted in the case of the hospitalized oncological patient. Recognizing the patients at risk of developing TLS is essential, and so is the prophylactic treatment. The initiation of treatment for TLS is a medical emergency that must be addressed in a multidisciplinary team (oncologist, nephrologist, critical care physician) in order to reduce the risk of death and that of chronic renal impairment. TLS can occur spontaneously in the case of high tumor burden or may be caused by the initiation of highly efficient anti-tumor therapies, such as chemotherapy, radiation therapy, dexamethasone, monoclonal antibodies, CAR-T therapy, or hematopoietic stem cell transplantation. It is caused by lysis of tumor cells and the release of cellular components in the circulation, resulting in electrolytes and metabolic disturbances that can lead to organ dysfunction and even death.

cancer chemotherapy toxicity tumor lysis syndrome

1. Introduction

Tumor lysis syndrome (TLS) is the result of a series of events leading to the rapid death of a high number of malignant cells. Lysis of these cells leads to the release of intracellular ions and metabolic byproducts into the bloodstream, resulting in hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. All these disturbances may cause serious complications such as AKI, cardiac arrhythmias, seizures, and even death.

TLS is an oncological emergency with high morbidity and mortality, especially if the diagnosis is delayed and treatment measures are not instituted promptly [1]. The most important aspect is to rapidly identify the patients at risk for TLS, in order to start the proper prophylactic and curative treatment. It commonly occurs in patients with high-grade hematological malignancies, such as acute leukemia and Burkitt's lymphoma, but also in large and rapidly growing solid organ tumors, especially after starting chemotherapy [2][3]. It is a life-threatening condition, being responsible for increasing the in-hospital mortality of the cancer patient by up to 79% in cases of acute myeloid leukemia (AML) during induction therapy [4][5]. It may occur either spontaneously, or after antineoplastic therapy such as conventional chemotherapy, corticosteroids, molecular-targeted therapy, immunotherapy, and even after radiotherapy and chemoembolization [6][7][8][9][10][11][12][13][14][15][16][17].

2. Definition and Classification

Hande and Garrow classified TLS in 1993 in two categories: laboratory and clinical TLS [18]. They used some specific parameters of which variation are usually observed during the first four days after starting antineoplastic therapy. Their definition was not including patients with spontaneous TLS, and it was modified by Cairo and Bishop in 2004 by summing up the clinical and laboratory changes that appear within 3 to 7 days after the initiation of chemotherapy, thus including patients who already have TLS at presentation, as well as those who are developing it later on (**Table 1**) [19]. Additionally, it is necessary to exclude other causes of AKI.

Table 1. Cairo–Bishop criteria for defining tumor lysis syndrome (modified after [19]).

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

TLS—tumor lysis syndrome.

Howard and colleagues made several amendments to the Cairo–Bishop definition in 2011:

- changes of the laboratory parameters must be simultaneous within 24 h because the patient may develop one abnormality, and later on another, unrelated to TLS (e.g., hypocalcemia associated with sepsis);
- symptomatic hypocalcemia has to be a criterion for clinical TLS, even when the decrease in calcium level is less than 25% of baseline;

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a 25% variation of a parameter is significant for the diagnosis only if it causes symptoms or if the value is not within the normal range [2].

Moreover, according to some authors [6], the definition of renal dysfunction has to be the same as the AKI definition, meaning an increase in serum creatinine by ≥0.3 mg/dL or an increase to ≥1.5 times baseline or oliguria (defined as a decrease in urine output below 0.5 mL/kg/h for 6–12 h) [20]. This will help to distinguish the patients with pre-existing kidney impairment from those who develop AKI secondary to TLS.

3. Pathogenesis

Pathogenic mechanisms are based on the release of potassium, phosphorus, and nucleic acids during tumor cell lysis in quantities higher than the body’s homeostatic mechanisms (**Figure 1**).

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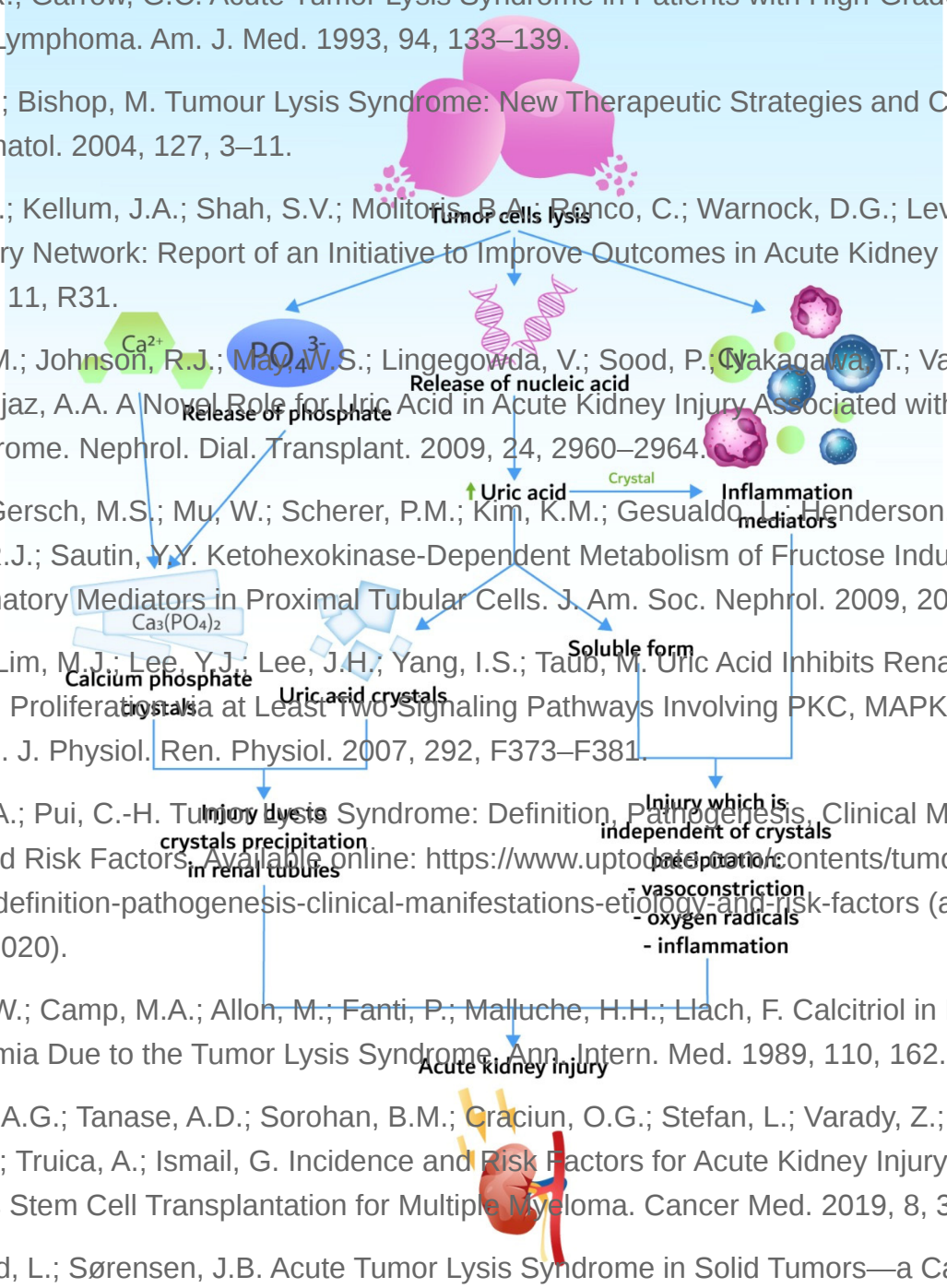

Figure 1. Pathogenesis of tumor lysis syndrome, resulting in acute kidney injury.

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3.1. Hyperuricemia

Nucleic acids (adenosine monophosphate—AMP, guanosine monophosphate—GMP) are metabolized into adenine and guanine and then to hypoxanthine and xanthine, which is finally converted into uric acid under the influence of xanthine oxidase. In mammals, uric acid is further metabolized into allantoin (a molecule 5 to 10 times more soluble than uric acid) that is excreted by the kidneys. This catabolic pathway needs the presence of urate oxidase (OU), an enzyme lacking in humans and higher primates (**Figure 2**). Due to abnormal high levels, uric acid

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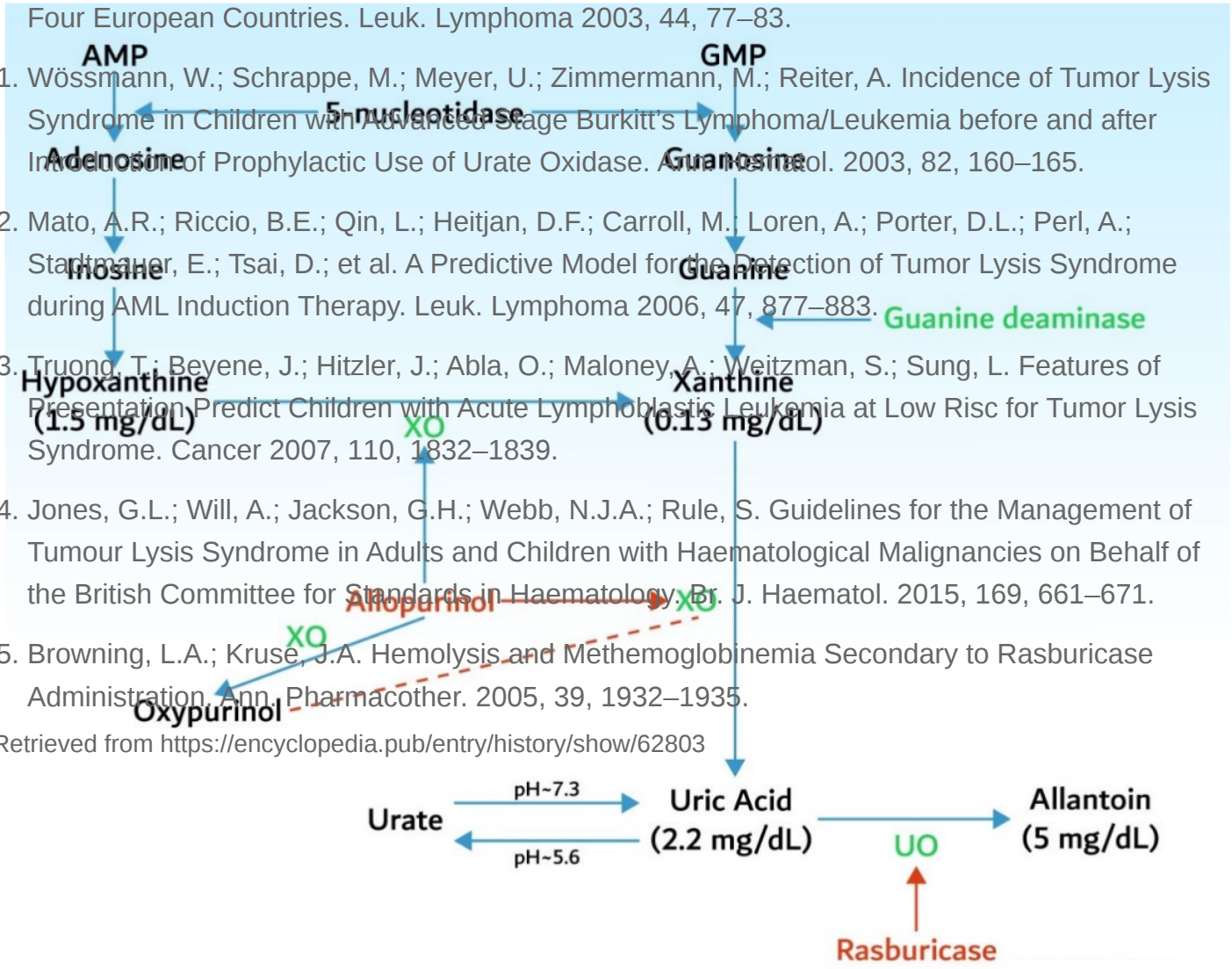

Figure 2. Uric acid metabolism and mechanisms of action of hypouricemic drugs. AMP—adenosine monophosphate; GMP—guanosine monophosphate; XO—xanthine oxydase; UO—urate oxydase.

Tubular obstruction leads to progressive increase in proximal and distal tubule pressure and therefore to increased peritubular capillary pressure and vascular resistance. Furthermore, high levels of uric acid cause smooth muscle cells to release cytokines that cause systemic inflammatory response syndrome: monocyte chemotactic protein 1 (MCP1), tumor necrosis factor (TNF-α), mitogen-activated protein kinases (MAPK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) [22]. Proliferation of proximal tubular cells and endothelial cells is inhibited once renal injury is produced [23].

3.2. 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.

3.3. Hyperphosphatemia and Hypocalcemia

Cell lysis releases significant amounts of phosphate, leading to hyperphosphatemia. As in the case of hyperkalemia, hyperphosphatemia is even more severe in the setting of pre-existing kidney impairment. Malignant cells have a four times higher level of phosphate than normal cells [24].

Another mechanism of phosphate toxicity is the binding of the calcium to the phosphate. Hypocalcemia may become symptomatic, causing neuromuscular excitability with tetany, seizures, arrhythmia, and death. Hypocalcemia may persist even after the resolution of hyperphosphatemia, possibly due to 1.25-vitamin D deficiency [25].

4. Epidemiology

The incidence of TLS varies from sporadic cases up to high incidence (**Table 2**). However, even in tumors with low risk for TLS, the patient should be closely monitored as diseases such as multiple myeloma may develop TLS due to highly efficient modern anticancer therapy [26].

Table 2. Solid tumors associated with tumor lysis syndrome [27].

Germ cell tumors
Neuro- and medulla blastomas
Small cell carcinoma and other lung tumors
Breast, ovarian, and vulvar neoplasms
Hepatoblastoma and hepatocellular carcinoma
Colorectal and gastric carcinoma
Melanoma
Sarcoma

5. Identification of Patients at Risk

TLS is associated with significant morbidity and mortality. Proper assessment of the patients with appropriate risk stratification is of major importance for a more efficient therapeutic approach. Several risk-stratification models for

TLS have been developed [28][29], most of them taking into account different patients' characteristics (including other comorbidities) and type of neoplasia (**Table 3**).

Table 3. Risk factors for tumor lysis syndrome [5][30][31][32][33].

Tumor Risk Factors	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.

6. Tumor Lysis Syndrome Management

6.1. Prophylaxis

The key of 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 with the following frequency:

- 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 the treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

6.2. Treatment

Once established, TLS necessitates a 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/m^2/h for adults and 4 mL/kg/h for children. Urine alkalinization is not recommended (level 1C recommendation) [34].

It is recommended to administer rasburicase and not xanthine oxidase inhibitors, since they do not have any effect on the uric acid that has already been produced. The only indications for xanthine oxidase inhibitors are known rasburicase allergy and G6PD deficiency [34]. 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. In contrast to the prophylactic treatment, when administration of low doses of rasburicase is supported by multiple studies, there are not enough data to support a fixed, low dose of rasburicase compared to weight adapted doses when dealing with an already constituted TLS. Some studies still recommend a fixed, single dose of 6 mg, which was found to be as effective as the weight-adapted dose [35]. Therefore, for financial reasons, this alternative treatment may be reasonable and suitable for daily administration.

Renal Replacement Therapy

The necessity for renal replacement therapy (RRT) decreased dramatically in the era of hypouricemic drugs, especially in the countries where rasburicase is available for the prevention and treatment of TLS. 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 are:

- daily hemodialysis;
- continuous veno-venous hemofiltration;
- combination of intermittent hemodialysis and continuous hemofiltration/hemodiafiltration for an efficient clearance of phosphate, which is time dependent. These techniques use dialysis membranes with large pores, which allow for rapid clearance of molecules that otherwise are not efficiently removed by conventional hemodialysis.

Peritoneal dialysis is not adequate, because it offers a less efficient clearance of uric acid and phosphate. Moreover, patients may associate abdominal complications related to neoplasia (peritoneal carcinomatosis, compartment syndrome), which are contraindications for this procedure.

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