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UNDERSTANDING THE DISEASE

Understanding tumor lysis syndrome

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Tumor lysis syndrome (TLS) is a life-threatening condition in patients with extensive and chemosensitive malignancies. It usually occurs as a consequence of anticancer treatments, although it can also arise spontaneously (in up to a third of TLS cases) [1, 2]. TLS results from the rapid destruction of malignant cells, whose intracellular content (ions, proteins, and metabolites) is consequently released into the extracellular space. Potassium, calcium, phosphates, and deoxyribonucleic acid (DNA), which are present in high concentrations in malignant cells, are released into the extracellular space, leading to hyperkalemia, hyperphosphatemia, and subsequent hypocalcemia. DNA catabolism leads to the release of adenosine and guanosine, which are converted into xanthine and then uric acid. TLS occurs when renal clearance is insufficient to handle this metabolite release. The above-described metabolic disturbances may contribute to the development of acute kidney injury (AKI), thereby further decreasing metabolite clearance and increasing TLS symptoms and consequences. The formation of uric acid crystals in the renal tubules has been described as the main mechanism underlying AKI, other causes being calcium-phosphate deposition and crystal-independent pathways involving systemic inflammatory responses (Fig. 1) [3].

Because TLS-induced AKI decreases the chances of chemotherapy being optimally effective, it reduces the likelihood of achieving complete remission of the underlying malignancy and is associated with high mortality rates [2, 4, 5]. Although kidney is the main affected organ during TLS, systemic inflammatory response mimicking sepsis and multiple organ failure may occur [3].

Current definitions of TLS follow the classification developed by Cairo and Bishop [6]. Accordingly, laboratory TLS refers to the occurrence of metabolic disturbances (hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia) within the three days prior to or the seven days following the administration of cancer chemotherapy, while clinical TLS refers to the presence of clinical manifestations (cardiac, renal, or neurological) in a patient with laboratory TLS. However, despite these definitions, TLS is not a straightforward diagnosis, for several reasons. First of all, uremic syndrome resulting from other causes may mimic TLS. In this setting, electrolytic abnormalities kinetic (i.e increase of phosphatemia, kaliemia and lacticodehydrogenase levels) may help in differentiating TLS-induced AKI from AKI due to other etiologies. Indeed, in TLS, hyperphosphatemia and hyperkalemia precede the appearance of AKI; furthermore, intracellular levels of phosphorus in tumor cells are four times higher than the levels found in normal cells. A rapid course of hyperphosphatemia, which parallels the rapid increase of lactico-dehydrogenase and hyperuricemia, will suggest that TLS is involved in the mechanism of AKI. It is also necessary to be aware that TLS may be present prior to the detection of cancer, or conversely that its onset may be delayed in patients receiving targeted therapies or immunotherapies [7].

Early recognition of patients at high risk of TLS is necessary in order to allow adequate monitoring and initiation of preventive measures. High-risk patients usually have a high-grade hematological malignancy (acute leukemia or high-grade lymphoma) and a large tumor burden (hyperleukocytosis or bulky disease) [8]. However, an increasing rate of TLS has been described in indolent tumors (solid tumors, chronic lymphoid leukemia and myeloma) treated with targeted therapies [7]. Despite routine urate oxidase therapy, TLS may develop in up to two-thirds of high-risk patients, leading to AKI in half of them [2].

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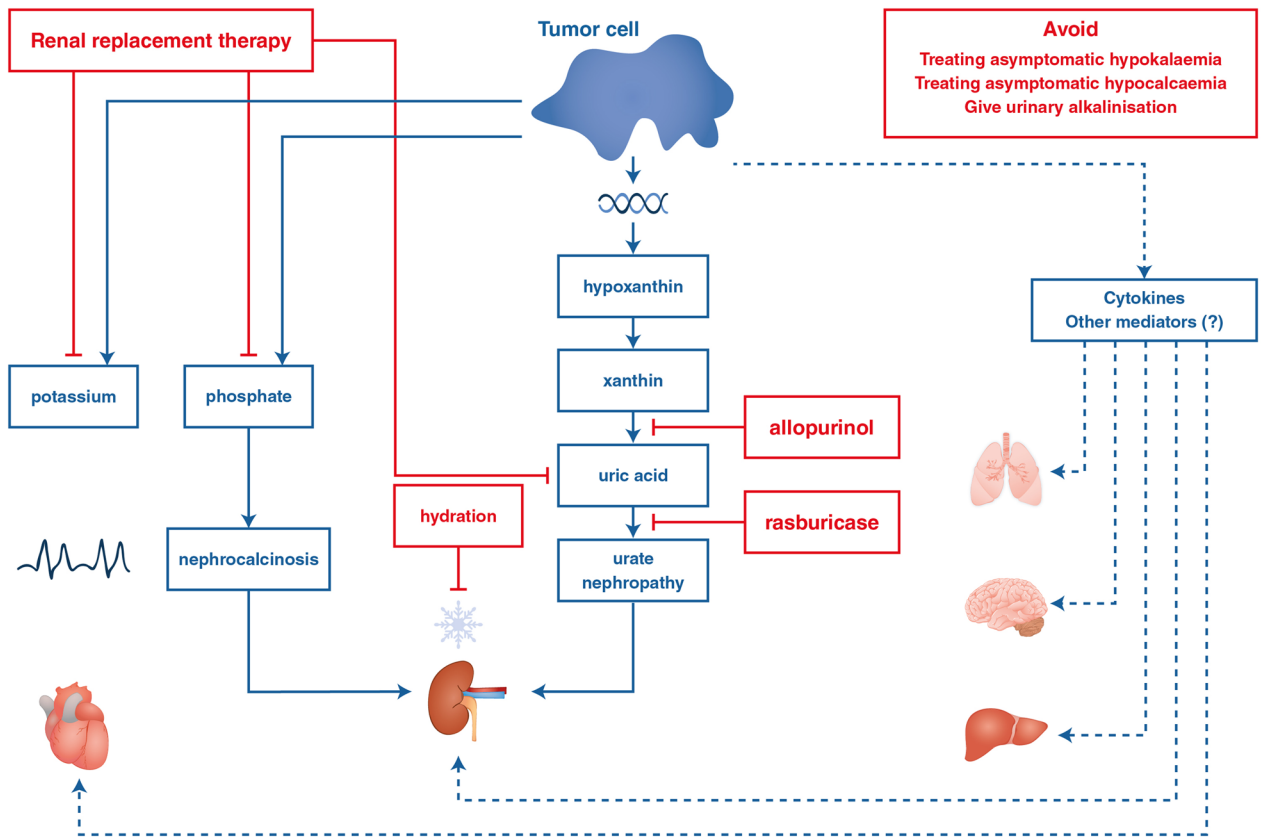

Fig. 1 Mechanisms of TLS-induced multi-organ failure. Tumour cells release intracellular potassium, phosphate and Deoxy-ribo-Nucleic Acid (DNA) into the extracellular space. Potassium may induce cardiac arrhythmia. Phosphate and calcium may precipitate together and induce nephrocalcinosis. DNA is metabolised into adenosine and guanosine, which are converted into xanthine and then uric acid. Uric-acid crystal formation in the renal tubules has been described as the main mechanism of AKI. These metabolic disturbances may lead to AKI. Moreover, AKI increases hyperkalaemia, hyperphosphatemia and hyperuricemia. Crystal independent mechanisms of AKI and multi-organ failure are poorly understood and may involve other metabolites and cytokines secreted by tumour cells. Hydration maintains a high urinary output to enhance uric acid and phosphate clearance. Renal replacement therapy may be effective in controlling the metabolic disturbances and preventing AKI. Allopurinol, a structural isomer of hypoxanthine inhibits the conversion of xanthine to uric acid. Rasburicase is a recombinant urate oxidase that converts uric acid into allantoin, carbon dioxide, and hydrogen peroxide

Prevention and treatment of TLS

Hydration

Extracellular fluid volume expansion with saline (3L/m^2 per day) is the cornerstone of TLS prevention and treatment [1, 9]. The theoretical rationale for aggressive intravenous hydration is that this approach will dilute the intracellular components that are released into the blood, increase urinary output, and preserve renal function. However, in the absence of obvious volume depletion, the concept that intravenous hydration can prevent, or reduce the severity of AKI, or accelerate renal recovery is not demonstrated by robust clinical data. Moreover, volume expansion carries a risk of fluid overload with the attendant clinical consequences. Careful attention should be paid to elderly patients with underlying chronic heart or kidney disease. Urinary alkalinization is poorly efficient [10], increases the risk of calcium-phosphate nephropathy, and is therefore no longer recommended [9].

Diuretics

The use of diuretics has been advocated by some authors in order to enhance urinary flow rate and decrease the risk of crystal precipitation [1]. However, this approach

has never been specifically studied and the hemodynamic changes associated with diuretics may compromise kidney function in these patients.

Hypouricemic agents

Allopurinol, a structural isomer of hypoxanthine, inhibits the conversion of xanthine to uric acid. It is the drug of choice for prophylaxis in patients with low/intermediate risk of TLS, but it may be less effective than rasburicase in patients with hyperuricemia and already formed urate crystals [8, 9, 11]. Rasburicase is a recombinant urate oxidase that converts uric acid into a hydrosoluble compound: allantoin. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, as it may induce severe methemoglobinemia and hemolytic anemia. Rasburicase is effective in decreasing uric acid concentrations within four hours [11], but no study has shown it to impact on AKI prevention, the need for renal replacement therapy (RRT), or mortality. British guidelines recommend a dose of 0.2 mg/kg of rasburicase [9]. However, a fixed dose of 3 mg in a single administration followed by close monitoring has been proven safe and efficient [12]. These same guidelines recommend the use of rasburicase in established TLS and for prevention in high-risk patients and intermediate-risk patients with hyperuricemia [9]. The possible role of febuxostat, another oxidase inhibitor, remains to be defined.

Prevention of nephrocalcinosis

Knowledge of the role of nephrocalcinosis in the pathophysiology of TLS is based only on very old case reports [13, 14] of patients with extreme hyperphosphatemia, published when urinary alkalinization was commonly used. The impact of hyperphosphatemia-induced nephrocalcinosis on AKI in TLS has yet to be evaluated in the era of new prevention strategies. Nevertheless, in order to avoid calcium-phosphate precipitation, beyond fluid expansion using saline, asymptomatic hypocalcemia should not be treated [9].

Renal replacement therapy

There is a lack of studies concerning the indications for, and modalities and timing of, RRT in TLS. In view of the ongoing release of intracellular content by the tumor cells, continuous RRT has been preferred to intermittent hemodialysis in order to reduce the risk of rebound hyperphosphatemia and hyperkalemia. On the other hand, conventional hemodialysis is superior to hemofiltration for rapid clearance of potassium and phosphate. Some authors have suggested that early hemodialysis, immediately followed by continuous RRT or prolonged hemodialysis sessions, might be envisaged [15]. In the absence of life-threatening metabolic disturbances, the optimal timing for initiating RRT in TLS-induced AKI is unknown. A stepped wedge cluster randomized controlled trial on the benefits of prophylactic RRT in high-risk patients might provide guidance for intensivists with regard to the management of these patients.

The role of the intensivist in the management of high-risk patients is primordial. Chemotherapy can be safely administered in the ICU, and hematological patients at high risk of complications, including TLS, should preferably be admitted before the onset of organ failure. Close monitoring of TLS patients includes measurement of serum potassium, calcium, phosphate, urea, creatinine, and uric acid, at least every 6 h [8]. Close collaboration between intensivists, oncologists, and hematologists is also of primordial importance. Indeed, in high-risk patients, one should discuss different "debulking" strategies; in acute myeloid leukemia with high white blood cell count, for example, a possible strategy might be to gradually escalate doses of chemotherapy or oral hydroxyurea in order to gradually lower the white blood cell count prior to intensive chemotherapy, with a view to avoiding massive release of intracellular content [16].

In conclusion, TLS may lead to AKI and multiple organ failure. The pathophysiology of TLS-induced AKI includes both crystal-dependent and crystal-independent mechanisms that are currently poorly understood. 'Preventive' ICU admission of high-risk patients would allow better management of electrolyte disturbances, hydration, and anticancer therapeutic strategies, as well as close monitoring of these patients.

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Compliance with ethical standards

Conflicts of interest
L Zafrani has received a research grant from Jazz Pharma. Dr. Darmon reports grants from MSD, personal fees from Gilead-Kite, personal fees from Astelas, outside the submitted work; Dr. CANET reports personal fees from GILEAD, outside the submitted work.

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