REVIEW

Tumor lysis syndrome in intensive therapy: diagnostic and therapeutic encare

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Abstract
The tumor lysis syndrome (TLS) is a life-threatening complication caused by the massive release of nucleic acids, potassium and phosphate into the blood. This complication is the result of tumor cell lysis, which may occur due to treatment of drug sensitive and is characterized by rapid capacity of proliferation, that is often hematological origin. Moreover, the TLS can be observed before starting the treatment due to spontaneous tumor cell death, and frequently worsens when chemotherapy is initiated. TLS has high mortality, so that its prevention continues to be the most important therapeutic measure. In the intensive care unit (ICU), physicians should be aware of the clinical characteristics of TLS, which results in severe electrolyte metabolism disorders, especially hyperkalemia, hyperphosphatemia and hypocalcemia, and acute kidney injury which is a major cause of ICU mortality. An adequate strategy for the management of the TLS, combining hydration, urate oxidase, and an early admission to ICU can control this complication in most patients. The aim of this review is to provide diagnostic tools that allow to the ICU physician to recognize the population at high risk for developing the TLS, and outline a proper strategy for treating and preventing this serious complication.

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KEYWORDS
Tumor lysis;
Acute kidney injury;
Critically ill patient

PALABRAS CLAVE
Lisis tumoral;
Fallo renal agudo;
Paciente crítico

Síndrome de lisis tumoral en terapia intensiva: encare diagnóstico y terapéutico

Resumen
El síndrome de lisis tumoral (SLT) es una complicación potencialmente letal provocada por la liberación masiva de ácidos nucleicos, potasio y fosfato hacia la circulación sistémica. Este cuadro es el resultado de la lisis celular de neoplasias, con frecuencia hematológicas, las cuales se caracterizan por una rápida capacidad de proliferación y alta sensibilidad a fármacos. Por otra parte, el SLT se puede observar por muerte celular espontánea previo al inicio del tratamiento citorreductor, agravándose luego de iniciada la quimioterapia. El SLT presenta una alta

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Introduction

Cancer patients are increasingly admitted to the Intensive Care Unit (ICU). According to the results of the study published by Taccone et al., in 198 European ICUs, 15% of the admitted patients presented neoplastic disease at the time of admission. On the other hand, in recent years there has been marked improvement in the prognosis of patients with solid and hematological malignancies admitted to the ICU - the current mortality figures being 21% for patients with solid tumors and 45% for those with hematological malignancies.

This new reality makes it necessary for intensivists to become increasingly familiarized with the complications inherent to both the neoplasm and to the treatment strategies employed. In this context, the evaluation, recognition and management of tumor lysis syndrome (TLS) is a crucial issue, since established prevention and treatment strategies are available that can significantly reduce the morbidity-mortality of this syndrome.

Tumor lysis syndrome, described in the year 1929 by Bedrna and Polcak, is a clinical condition produced by the massive and sudden release into the bloodstream of intracellular products (nucleic acids, potassium and phosphates) secondary to tumor cell death or lysis. In clinical practice, TLS normally manifests as a consequence of cytoreductive treatment (chemotherapy, radiotherapy), though it must be underscored that the syndrome may manifest before the start of such treatment.

TLS produces severe and potentially fatal consequences, affecting mainly water-electrolyte metabolism and the renal parenchyma. The ionic disturbances most frequently associated with TLS are hyperpotassemia, hyperphosphatemia and hypocalcemia. Acute renal failure in the context of this syndrome is of multifactorial origin, with the accumulation of uric acid crystals in the renal tubuli and alterations in renal perfusion.

In this context, correct management involves adequate fluid replacement, urine alkalization, the use of uricemia-lowering agents, and renal replacement therapies (RRTs). All these therapeutic measures form an essential part of the preventive and management strategy applied to TLS in the ICU.

The main interest of the present review is that it offers diagnostic tools allowing the intensivist to recognize patients at risk of developing TLS, and to establish an adequate preventive and treatment strategy in cases of tumor lysis syndrome.

Diagnosis

Tumor lysis gives rise to the release of intracellular products (nucleic acids, potassium and phosphates) into the bloodstream, which can cause serious disturbances in the internal medium – particularly severe ionic alterations and acute kidney damage.

Hande and Garrow developed a TLS classification system based on the clinical manifestations and laboratory test findings. This classification has made it possible to define those patients who might derive benefit from specific treatment. In turn, in the year 2004 Cairo and Bishop presented a first modification of this classification, establishing two well differentiated clinical entities (Table 1): 1) LTLS, or laboratory tumor lysis syndrome (characterized by at least two altered laboratory test parameters); and 2) CTLS, or clinical tumor lysis syndrome (LTLS associated to at least one clinical parameter).

Table 1 Criteria defining tumor lysis syndrome according to Cairo-Bishop

<table>
<thead>
<tr>
<th>Laboratory definition</th>
<th>Clinical definition</th>
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<tbody>
<tr>
<td>Uric acid ≥ 476 mmol/l (8 mg/dl) or 25% increase versus basal value</td>
<td>Plasma creatinine ≥ 1.5 ULN (adjusted for age)</td>
</tr>
<tr>
<td>Potassium ≥ 6.0 mmol/l or &gt;25% increase versus basal value</td>
<td>Arrhythmias / sudden death</td>
</tr>
<tr>
<td>Phosphorus ≥ 1.45 mmol/l or 25% increase versus basal value</td>
<td>Seizures</td>
</tr>
<tr>
<td>Calcium ≤ 1.75 mmol/l or 25% decrease versus basal value</td>
<td>ULN: upper limit of normal.</td>
</tr>
</tbody>
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The different degrees of severity of the syndrome are defined by the magnitude of the clinical and laboratory test alterations (Table 2).

### Incidence

TLS is most often seen in patients with acute lymphoproliferative syndromes such as acute lymphoblastic leukemia, Burkitt lymphoma and myeloid leukemia. Likewise, the syndrome can manifest during the treatment of solid tumors such as sarcomas, ovarian cancer or small-cell lung cancer. In general, the development of TLS in the presence of solid tumors is associated with increased mortality, due to a lesser degree of clinical suspicion that implies failure to adopt the opportune preventive measures. Tumor lysis is often associated to the start of cytoreductive treatment (chemotherapy or radiotherapy), though spontaneous presentations have also been described. This latter situation may occur in up to one-third of all cases, but is exceptional in patients with solid tumors.

The reported incidence of this serious complication varies greatly (LTLS 0.42%-42%, CTLS 0.33%-27%), and depends on the type of neoplasm, the chemotherapy used, and the adoption or not of an adequate preventive strategy. In elderly patients, the presence of TLS is more serious, due to the existing comorbidities—fundamentally chronic renal failure and heart disease—which preclude adequate volume replacement as preventive strategy.

### Risk factors

The risk of developing TLS is related to patient parameters, the background disease, the biochemical findings, and treatment (Table 3).

Based on the above, it is possible to define risk categories for the development of TLS (Table 4), allowing adoption of the most appropriate management strategy in each case. It is therefore important for the medical team in the ICU and in the Oncological Hematology Unit to be able to perform this risk assessment with a view to offering the best treatment strategy.

### Etiopathogenesis

The etiopathogenesis of TLS involves the intervention of the different cellular elements that penetrate the bloodstream as a result of tumor lysis—particularly nucleic acids (hyperuricemia), phosphorus (hyperphosphatemia) and potassium (hyperpotassemia).
The purine bases of the nucleic acids are metabolized into hypoxanthine, which in turn is converted to uric acid. This metabolite is scantily soluble in water and is eliminated through the kidneys at a rate of 500 mg/day. When the uricemia levels exceed 420 µmol/l (7 mg/dl), uric acid precipitates and causes renal tubular obstruction. Two factors favor the tubular precipitation of uric acid: an acid urine pH value and hypovolemia.

The intracellular levels of phosphates in the tumor cells may be several times higher than in normal cells. After the appearance of hyperphosphatemia, urine excretion increases while tubular reabsorption concomitantly decreases. These adaptive mechanisms are quickly overwhelmed, however, and so hyperphosphatemia is a constant finding in TLS. The increase in serum phosphorus in turn increases the Ca x P product, which favors two important events:  

a) The formation of so-called phosphocalcium products, which precipitate in the renal tubuli and cause kidney damage.

b) Hypocalcemia.

Potassium translocation towards the extracellular compartment produces hyperpotassemia, which can represent a serious and potentially fatal complication. A number of factors contribute to the cardiovascular toxicity of hyperpotassemia, including particularly the rate of onset of hyperpotassemia, and the existence of renal damage.

Renal failure is one of the main complications of TLS. It is therefore essential to know the mechanisms implicated in the etiopathogenesis and physiopathology of renal damage associated to TLS. These mechanisms include three major groups of phenomena:

a) Dependent upon crystal formation (tubular obstruction due to precipitation of the calcium phosphate and urate crystals).

b) Independent of crystal formation (mechanisms involving autoregulation of the renal blood vessels and the proinflammatory and renal vasoconstrictor effects of the urates).

c) Related to antineoplastic treatment (nephrotoxicity of certain cytostatic agents such as the asparagines, busulfan, bortezomib, cisplatin, daunorubicin, mercaptopurine, methotrexate, and rituximab).

### Clinical manifestations

The clinical manifestations of TLS are the same as those associated to each of the internal medium disturbances that characterize the syndrome (hyperuricemia, hyperpotassemia, hyperphosphatemia and secondarily hypocalcemia). The most serious manifestations are observed in the first three or four days after the start of chemotherapy, immunotherapy or radiotherapy.

Uricemia > 7.5 mg/dl (446 µmol/l) produces gastrointestinal (nausea, vomiting, diarrhea, anorexia) and renal manifestations (oliguric or anuric acute renal failure).

The critical manifestations of hyperpotassemia (serum concentration > 5.0 mEq/l) in relation to the cardiovascular system comprise severe arrhythmias (tachycardia and ventricular fibrillation), which constitute a genuine medical emergency. Based on the criteria established by the National Kidney Foundation, the accepted adequate blood phosphate levels are under 4.5 mg/dl (1.45 mmol/l).

The clinical picture associated to hyperphosphatemia in general is not particularly manifest, unless it is combined with hypocalcemia, in which case the predominant clinical manifestations correspond to the latter alteration.

The clinical manifestations of hypocalcemia in turn depend not only on the calcium ion levels but also on the rate of onset of hypocalcemia. These manifestations are a consequence of increased neuromuscular and cardiac excitability, and include tetany, paresthesias, muscle spasms and seizures. The cardiovascular manifestations in turn include prolongation of the ST-segment and QT-interval – the latter being a risk factor for the development of severe ventricular arrhythmias (polymorphic ventricular tachycardia) and sudden death. Lastly, the negative inotropism contributes to the development of heart failure, arterial hypotension and cardiogenic shock.

The early identification of acute renal failure has prognostic implications in TLS. Given the rate of renal failure onset in these patients, the manifestations fundamentally will consist of the already examined ionic disorders and hypervolemia. In all these patients it is essential to monitor renal function and diuresis, with the purpose of ensuring the early identification of acute damage or failure.
Treatment

Patients with established TLS or at moderate to high risk of developing the syndrome stand to benefit from admission to the ICU.

Fluid replacement is the initially established treatment strategy - 0.9% sodium chloride solution (physiological saline) being the fluid of choice. This is the central element in the prevention and treatment of TLS. In general terms, the replacement dose should be 3 liters/m²/day, though adjustment to the individual characteristics of the patient is required. Fluid replacement must be carried out under strict hemodynamic monitoring (arterial pressure, heart rate, central venous pressure, SVo₂, diuresis or pulmonary wedge pressure) – the main objective of water replacement being the achievement of diuresis > 1 ml/kg/hour. However, it must be considered that in the population at greatest risk of developing TLS (i.e., oncohematological patients), it is often not possible to carry out invasive hemodynamic monitoring due to the increased risk of bleeding or infection; as a result, strict hourly diuresis control is a fundamental monitoring parameter in these individuals.

Fluid replacement increases renal tubular flow, stimulates diuresis and those promotes and favors the elimination of urates and phosphates – avoiding their precipitation within the tubular lumen. With the purpose of increasing diuresis, use can be made of loop diuretics (furosemide), though these must be administered once the hypovolemia has been corrected, i.e., such drugs never constitute an initial treatment option.

Once hypocalcemia has been diagnosed, treatment with calcium chloride or gluconate will depend on the levels of ionic calcium and on the presence of clinical manifestations such as arrhythmias, seizures, muscle cramps or tetany.

The treatment of hyperphosphatemia is indicated when the latter is severe, as defined by the clinical manifestations and acute course. Such treatment is based on volume expansion by administering isotonic 0.9% sodium chloride solution to favor the renal excretion of phosphorus. Phosphorus-binding solutions (aluminum hydroxide, calcium carbonate) are a possible treatment option, though in the context of acute renal failure renal replacement therapy (RRT) is the most effective choice for the management of this serious complication. The duration of RRT is the determining factor in phosphate elimination.

The solubility of uric acid increases more than 10 times (from 15 mg/dl to 200 mg/dl) when the pH changes from 5.0 to 7.0. Urine alkalinization thus increases uric acid excretion, preventing its tubular precipitation. However, urine alkalinization is unable to increase xanthine elimination. Therefore, after treatment with allopurinol, xanthine and calcium phosphate precipitation may occur, with tubular obstruction and the worsening of prior renal damage. Another complication inherent to alkalinization is the worsening of pre-existing hypocalcemia. Due to these adverse effects, urine alkalinization is currently not recommended on a systematic basis. Lastly, fluid replacement has been compared with other therapies, and has been found to be superior to alkalinization.

Allopurinol acts through the competitive inhibition of xanthine oxidase, resulting in the inhibition of uric acid production (Fig. 1). However, its use has some disadvantages.

Table 5 Differences between allopurinol and Rasburicase

<table>
<thead>
<tr>
<th>Presentación</th>
<th>Allopurinol</th>
<th>Rasburicase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechánico de acción</td>
<td>Inhibe la oxidasa de xantina</td>
<td>Transforma ácido úrico en allantoina</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>&gt;2 days</td>
<td>4 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>1-2 hours</td>
<td>19 hours</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Diuréticos, fármacos antineoplásicos, dicoumarina</td>
<td>None</td>
</tr>
<tr>
<td>Dose adjustment</td>
<td>Nécessaire en caso de insuficiencia renal</td>
<td>No necesario</td>
</tr>
<tr>
<td>Cost</td>
<td>Bajo</td>
<td>Alto</td>
</tr>
</tbody>
</table>
The use of RRT is a necessary management resource in critical patients with TLS. Some reference centers recommend its early implementation; consequently, RRT, and particularly hemodialysis, should be employed in all patients with persistent metabolic alterations despite fluid replacement measures, or in the case of renal acute renal damage.\(^{52}\) Another major indication for RRT is the presence of spontaneous tumor lysis, which as has been mentioned, implies the poorest functional prognosis.\(^{53}\) RRT in turn may be continuous, intermittent or a combination of both. The elimination of phosphates is more effective with hemodialysis than with hemofiltration, though there may be a considerable rebound effect with the former technique; as a result, the combination of both modalities may be indicated. According to Soares et al.,\(^ {54}\) the use of such dialysis techniques in patients with hematological malignancies should be decided early, since late application is associated to poorer functional results and greater patient mortality.\(^ {54}\)

Patients with established TLS have a formal indication for admission to the ICU. The management of this clinical condition is fundamented upon the following principles: a) fluid replacement; b) the administration of rasburicase; and c) the use of RRT. In this context, it is important to note that in the event of delayed RRT, acute renal failure in the setting of TLS may prove irreversible.\(^ {55,56}\)

### Strategy for the prevention of tumor lysis syndrome

It must be underscored that most of the proposed treatments are based on studies with a low level of evidence (level 5, grade D). As a result, new methodologically correct multicenter studies are needed to improve the limited current evidence.\(^ {57}\) Despite the above considerations, it is necessary to have well defined therapeutic protocols facilitating the management of these patients in the ICU and allowing optimum treatment results. The choice of a given therapeutic strategy is to be based on the risk of developing TLS, or on its severity once the syndrome has become established\(^ {58}\) (Fig. 2). Patients considered to be at moderate or high risk are therefore taken to have a formal indication for admission to the ICU. Such admission is fully justified for a period of no less than 72 hours. During admission, strict clinical and laboratory test monitorization is required. Treatment should be provided by a multidisciplinary team led by an intensivist and a

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**Table 6** Studies comparing the effectiveness of allopurinol and urate oxidase

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Population</th>
<th>No. of patients</th>
<th>Principal results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldman (2001)(^ {44})</td>
<td>Randomized, multicenter</td>
<td>Pediatric</td>
<td>52</td>
</tr>
<tr>
<td>Renyi (2007)(^ {50})</td>
<td>Prospective, multicenter, phase IV, comparing treatment with Rasburicase versus a historical allopurinol group</td>
<td>Pediatric</td>
<td>26</td>
</tr>
<tr>
<td>Sanchez-Tatay (2009)(^ {51})</td>
<td>Nonrandomized, observational</td>
<td>Pediatric</td>
<td>32</td>
</tr>
</tbody>
</table>
hematological oncologist. Considering the above, the intensivist must know the risk groups and salient features of TLS, and must be able to establish a correct therapeutic strategy.

In the low risk group, treatment consists of adequate fluid replacement via the intravenous route, administering isotonic 0.9% sodium chloride (saline) solution (3 liters/m²/day). The recommended parenteral hydration period includes the 48 hours prior to the start of chemotherapy, maintaining the same hydration rate for 72 hours.

Patients at intermediate risk benefit from admission to the ICU during 48-72 hours, with the purpose of ensuring strict clinical and laboratory test, and adapting therapy to the clinical evaluation results.

In this group correct intravenous hydration is to be provided with isotonic 0.9% sodium chloride solution. Likewise, treatment with allopurinol is indicated, at a dose of 300-400 mg/m²/day. Another pharmacological strategy involves the administration of a starting dose of rasburicase, followed by the maintenance of allopurinol.

Urine alkalization is another possible treatment option in this intermediate risk group (evidence level V, recommendation grade D). On the other hand, in the presence of uric acid concentrations > 7.5 mg/dl, the start of rasburicase treatment is recommended (evidence level II, recommendation grade B).

In the high risk group, patient management is fundamentally upon the following principles: a) parenteral hydration similar to that indicated in the lesser risk groups; b) rasburicase at a dose of 0.2 mg/kg/day during no less than 72 hours, and evaluating posterior treatment according to the uric acid levels obtained. Those patients with normal levels can be treated in the same way as the intermediate risk subjects, while those presenting sustained uric acid elevations should continue to receive rasburicase until the values have normalized. Lastly, RRT is a valid option recommended by some centers, though its use has declined since the introduction of rasburicase—currently being prescribed in less than 3% of all cases.

Continuation of chemotherapy

Evaluation of the start or continuation of chemotherapy must be established on an individualized basis. Patients at moderate to high risk of developing TLS should be admitted to the ICU before starting chemotherapy, in order to optimize clinical and laboratory test monitorization, and thus the corresponding prevention strategy. Most patients will require no interruption or delay in cytoreduction therapy. This issue should be extensively discussed between the intensivist and hematological or clinical oncologist, evaluating the possibility of reducing the treatment dose in certain cases. However, it must be underscored that reducing the chemotherapy dose may have a negative impact on the success of antitumor treatment, with a worsening of the middle- and long-term patient prognosis.

Figure 2 Therapeutic algorithm for tumor lysis syndrome. RRT: renal replacement therapy.

Prognosis

The prognosis of TLS depends on the severity of the condition. In this sense, spontaneous TLS represents the most serious presentation, with often fatal consequences. The appearance of acute renal failure is a prognostic indicator associated with high mortality. In turn, since the introduction of rasburicase, the prognosis of the more severe presentations of TLS has improved—though mortality remains high.

Lastly, it is important to mention that the long-term prognosis is fundamentally conditioned by the type of neoplasm and the corresponding possibilities for complete disease remission in each individual case.
Conflict of interest

The authors declare no conflict of interest.

References


