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Prevention, diagnosis and treatment of tumor lysis syndrome

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Abstract

Tumor lysis syndrome (TLS) is an acute, life-threatening condition that occurs either spontaneously or as a complication of cytoreductive antitumor therapy, and occurs in both children and adults. As a result of TLS, intracellular components are released into the extracellular space, leading to dysregulation of the body's homeostasis due to the accumulation of uric acid, phosphate and potassium ions, and hypocalcaemia, which may lead to cardiac arrhythmias, convulsions or kidney failure.

Key words: tumor lysis syndrome; prevention; treatment; chemotherapy

Introduction

Tumor lysis syndrome (TLS) is a metabolic disorder that occurs as a result of the rapid breakdown of cancer cells due to chemotherapy or radiotherapy. As a result, intracellular components are released into the extracellular spaces, which can result in life-threatening metabolic disorders [1,2]. Most often, the tumor lysis syndrome refers to neoplasms characterized by high chemosensitivity, high proliferation index and high cell mass. It is worth mentioning that, according to studies, acute tumor lysis syndrome may lead to the formation of embolic materials consisting of nuclear and cytoplasmic debris, which results in mechanical obstruction of the vascular bed [3,4].

The Cairo-Bishop criteria are used to identify and diagnose clinical tumor lysis syndrome (CTLS), taking into account the level of creatinine, the presence and type of arrhythmia, and the presence and severity of neurological disorders (seizures) [5,6]. In order to confirm the CTLS, it is necessary to confirm one of the above-mentioned criteria and at least two of the following laboratory exponents:

- serum uric acid level ≥8 mg/dL, or a 25% increase from baseline;
- serum potassium level ≥6 mmol/L, or a 25% increase from baseline;
- serum phosphate levels ≥6.5 mg/dL in children and ≥4.5 mg/dL in adults, or a 25% increase from baseline;
- serum calcium level ≤7 mg/dL, or a 25% decrease from baseline.

If the clinical criteria are not met and at least two laboratory criteria are met, the diagnosis is latent tumor lysis syndrome (LTLS). Importantly, the above-mentioned disorders must occur within 3 days before or up to 7 days after the start of chemotherapy [5].

Tab. 1 Cairo-Bishop criteria for diagnosis of TLS [5].

Laboratory criteria		Clinical criteria
Uric acid	≥8,0 mg/dL or 25% increase	• Creatinine 1,5 times the upper limit of normal • Cardiac arrhythmias • Seizures
Potassium	≥6,0 mmol/l or 25% increase	
Phosphorus	≥4,6 mg/dL or 25% increase	
Calcium	≤7,0 mg/dL or 25% increase	

Risk factors and the most common complications

Tumor lysis syndrome (TLS) is a complication of chemotherapy for several different types of cancer. It is most common in response to the treatment of hematopoietic malignancies, but there are also reports of TLS in people with solid tumors: small cell carcinoma, breast cancer, germ cell tumor, neuroblastoma or melanoma [7]. The risk factors in those cases are the presence of high tumor burden, metastases [8] as well as high tumor advancement and high sensitivity to therapy [9]. Tumor lysis syndrome is typically seen in patients with non-Hodgkin lymphoma (NHL) - especially Burkitt's lymphoma, acute lymphoblastic leukemia and acute myeloid leukemia (AML). TLS is found in 42% of NHL patients, with up to 6.1% developing clinically significant derangements. In the case of AML chemotherapy, the tumor lysis syndrome is present in approximately 17% of patients - 5% develop clinically significant complications [10].

In addition to the presence of abnormal haematological hyperplasia, there are also other risk factors for TLS. An analysis by Truong et al. Indicated: age ≥10 years (P <0.0001), splenomegaly (P <0.0001), mediastinal mass (P <0.0001) and initial WBC ≥20 x 10^9 / L (P <0, 0001) as independent TLS predictors. In the absence of any of these factors, the TLS negative prediction factor was 97%, with a sensitivity of 95% [11]. In addition, a number of other factors not directly related to the cancer and its advancement predispose to the development of the tumor lysis syndrome. Dehydrated patients with oliguria or anuria and preexisting renal dysfunction have a higher risk of developing electrolyte disturbances and acute kidney injury in TLS [10]. Similarly, pre-existing electrolyte disturbances (hyperuricemia, increased uric acid concentration) significantly contribute to the development of TLS [9].

According to the definition, the symptoms of tumor lysis syndrome occur up to 7 days after the initiation of cancer therapy [10], but most often they are observed 12-72 hours after administration of cytolytic chemotherapy [12]. As a result of the breakdown of cancer cells, significant amounts of potassium, uric acid and phosphorus are released into the bloodstream. The excess of these substances is normally excreted by the kidneys, but in the case of TSL, the hyperkalemia, hyperuricemia and hyperphosphatemia are too great to be compensated by renal filtration. Uric acid overload leads to its precipitation in the renal tubules and the deposition of crystals in collecting tubules and ureters, which results in acute renal failure (AKI) [13]. The development of AKI is also favored by the deposition of calcium and phosphate crystals in kidneys and by crystallizing xanthine [13]. Rapid changes in potassium levels are also very dangerous. Hyperkalemia in TLS leads to ventricular arrhythmias, which

may lead to cardiac arrest and even death [9,12]. The hypocalcaemia that occurs in TLS is most often secondary to phosphorus chelation. Calcium deficiency exacerbates the arrhythmia caused by hypokalaemia. It also leads to the development of tetany (calcium deficiency in muscles, inability to relaxate) and, in more advanced stages, seizures and death [14]. Low calcium levels may persist even after normalization of phosphorus levels due to vitamin D deficiency - often present in patients with cancer [14,15].

Methods of prevention

In patients at high or moderate risk of developing TLS, the importance of repeated monitoring of laboratory parameters at least twice a day, both before and 7 days after antitumor therapy, is indicated. Additionally, strenuous hydration and meticulous analysis of fluid balance (in order to maintain diuresis> 100mL / h) are the key to proper preventive management. The role of hydration in increasing renal tubular flow and promoting the elimination of urate and phosphate is indicated. Elderly patients or those suffering from heart failure should be given special care. If the desired diuresis cannot be achieved, it is advisable to use loop diuretics. One should remember about the interactions of thiazide diuretics with allopurinol and their influence on the level of uric acid, therefore their use in the prevention of TLS is not recommended [16–18].

Another important step in the prevention of TLS is the administration of hypouricemic agents, such as allopurinol or rasburicase. It should be remembered that allopurinol has no properties that reduce uric acid concentration before the initiation of treatment, therefore rasburicase is used in patients with pre-existing hyperuricemia. Prophylaxis of allopurinol should be induced in patients at moderate and high risk of TLS, and its use should be considered in patients at low risk. Prophylaxis with allopurinol should be performed up to three days before the start of chemotherapy [17,19].

It is also worth paying attention to urine alkalinization as a method historically recommended in therapeutic and preventive management. Nevertheless, evidence gathered in recent years has shown an impact of this approach on the accumulation of calcium phosphate in the renal tubules, particularly in hyperphosphatemia patients. Hence, urine alkalinization is not used in the prophylaxis or treatment of TLS [17].

Treatment

The most important elements of the treatment of clinically overt TLS is management of the life-threatening conditions, which consist of renal failure, arrhythmia and seizure, as

well as abnormalities causing them. The therapeutic approach differs – among other factors - depending on the current glomerular filtration rate. While intensive hydration in combination with diuretics might still be considered a prevention strategy, a total renal failure is usually a sign of a fully developed syndrome [20]. Although the indications for haemodialysis are the same as for other causes of renal failure in TLS, some authors suggest higher thresholds due to the possibility of more efficient normalization of the ions levels [5]. Continuous veno-venous hemofiltration was found to be safe and effective treatment even for paediatric patients with TLS [21]. Due to the occlusive nature of renal failure in TLS it's important to limit the crystallisation of uric acid in kidneys by either limiting its production with allopurinol or rasburicase, or inhibiting the crystallisation process itself [20]. Although allopurinol is more widely used, more and more evidence emerges on the superiority of rasburicase. A 2013 meta-analysis showed that single-dose rasburicase as well as daily dosing of rasburicase were significantly more efficient at lowering the uric acid levels in high TLS risk individuals [22]. The strategy of inhibiting the crystallisation of uric acid in kidneys remains controversial and is not routinely recommended, although the urine alkalinisation with the use of acetazolamide or sodium bicarbonate showed the ability of increasing the uric acid solubility [23].

The most dangerous abnormality in electrolyte levels is hyperkalemia, due to high risk of life-threatening arrhythmia. The temporary, yet very effective strategy to lower the potassium blood levels is IV injection of insulin and dextrose, which cause the shift of extracellular potassium into the cells. Hyperkalemia can be managed by administration of sodium polystyrene sulfonate as well. Extremely high levels of potassium can be reduced by dialysis, if necessary [24].

Seizures in TLS are caused by severe hyperphosphatemia and rapidly progressing hypocalcemia. Initial treatment of hyperphosphatemia usually includes extensive hydration, although phosphate binders such as aluminum hydroxide are utilised as well. Dialysis is an effective phosphate lowering factor as well [20]. Although hypocalcemia can often remain asymptomatic, infusion of calcium gluconate may be considered (only in justified cases, due to the risk of calcium-phosphate renal precipitation [5].

Summary

TLS is an example of an acute condition often present in cancer patients. When intracellular components are released into the extracellular space, the body's compensatory capacity is exceeded, leading to kidney and heart disorders, leading to their failure due to

excessive electrolyte concentrations. Hence, when planning anti-cancer therapy, attention should be paid to the risk of TLS in a given patient in order to implement appropriate prophylaxis or treatment. Preventive treatment is based on rehydration of the patient, monitoring of his vital functions and, if necessary, administration of hypoureximizing substances. Treatment in the event of overt or laboratory-confirmed TLS is based on restoring the concentrations of electrolytes and uric acid to physiological levels, controlling arrhythmias, seizures or conducting renal replacement therapy. Undoubtedly, due to the aging of the population, TLS will become an increasingly common problem. Thus, the key is the cooperation of healthcare professionals at every stage of anti-cancer treatment.

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