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Oncological emergencies: Tumor lysis syndrome

Stany nagłe w onkologii: Zespół rozpadu guza

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Tumor lysis syndrome (TLS) occurs as a result of massive lysis of malignant cells and release of intracellular contents into the systemic circulation. It can lead to hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. TLS is most commonly present after initiation of anticancer therapy but it can also develop spontaneously (STLS – spontaneous tumor lysis syndrome). In the article, pathophysiology, classification, risk factors and recommendations of management in TLS, with a special focus on solid tumors, are discussed. The keys to the identification of high-risk patients, prevention and management of TLS are included in presented guidelines.

Zespół rozpadu guza pojawia się w wyniku masywnej lizy komórek nowotworowych i uwolnienia ich zawartości do krwi. Może to prowadzić do hyperurykemii, hyperkaliemii, hyperfosfatemii i hypokalcemii. Jest on najczęściej powikłaniem leczenia przeciwnowotworowego, ale może również rozwinąć się spontanicznie. W artykule przedstawiono patofizjologię, podział, czynniki ryzyka i zalecenia dotyczące zespołu rozpadu guza, zwracając uwagę na jego występowanie w przypadku guzów litych. Zasady klasyfikacji grup ryzyka, prewencji i leczenia są zawarte w cytowanych wytycznych.

What is the tumor lysis syndrome?

Tumor lysis syndrome (TLS) is an oncological emergency. It is caused by the abrupt lysis of a large amount of malignant cells and the release of cellular constituents into the bloodstream. The massive release of nucleic acids, potassium, phosphorus and proteins can result in metabolic disturbances which may have severe clinical complications [1,2]. TLS leads to the death in 20–50 % of cases if undiagnosed or if diagnosed too late [3]. TLS has been recognized in association with leukaemia therapy since the 1870s. According to Malaguarnera and colleagues it was first reported by Bedrna and Polcák in adult patients with chronic leukaemia treated with irradiation in 1929 [4].

Etiology

TLS most often occurs after the initiation of cytoreductive treatment (mainly chemotherapy) [1,5]. It is one of the most frequent emergencies in oncohematology [1,2]. TLS may also occur in solid tumors, especially those with a high proliferative rate and high sensitivity to anticancer therapy e.g. neuroblastoma, germ cell tumors or small cell lung cancer [6]. Occasionally, it was observed in solid malignancies with poor response to antineoplastic agents like malignant melanoma, hepatocellular carcinoma, non-small cell lung cancer and carcinoma of the vulva [8]. The number of cases TLS in solid tumors seems to grow over the last decade. It is likely due to the availability of more effective anticancer therapies and an insufficient use of prophylactic regiments [9]. Differences in TLS between hematological malignancies and solid tumors are presented in Table I [8]. The most important risk factors for TLS are included in Table II [10]. The latest TLS risk classification system is presented in Table III [6]. In LRD (low risk disease), an approximate risk of developing TLS is less than 1%. In IRD (intermediate risk disease), the risk is approximately 1–5 %. In HRD (high risk disease), the risk exceeds 5%. In the case of renal dysfunction, patients with LRD become IRD. Patients originally with IRD are classified as HRD if renal dysfunction is noticed or if uric acid, phosphate or potassium levels are elevated [6].

Spontaneous tumor lysis syndrome (STLS), occurring in the absence of anticancer therapy is rare, but may have a worse prognosis due to delayed diagnosis [11,12]. It can also be the first manifestation of malignancy [13,14]. The etiology of STLS is not fully known. Various hypotheses are taken into consideration, e.g.: increased production of glucocorticoids, hypoperfusion of the tumor (worsened by pressure from the surrounding tissues or by hypovolaemia), hyperthermia or even surgical treatment of the tumor [11,13-15]. A disappearance of lymphadenopathy or an occurrence of necrosis in the tumor may be a clinical sign of STLS [11,12,15].

Pathophysiology

The rapid release of intracellular contents of malignant cells can overwhelm the excretory capacity of the kidneys and cause electrolyte and metabolic disturbances [16]. Hyperuricaemia usually occurs 48–72 hours after initiation of anticancer treatment [16]. Purine nucleic acids are released from broken tumor cells and metabolized into uric acid [2]. In Figure 1, a scheme of uric acid formation is presented. Due to the acidic pH and high concentration of uric acid, crystals are formed in the renal collecting ducts. Ob-

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struction of urine flow by these crystals leads to uric acid nephropathy and acute renal failure. Other factors which can promote acute renal failure in TLS are: volume depletion, precipitation of xanthine and/or calcium phosphate crystals, crystal-independent mechanisms, cytokine-mediated alteration in renal perfusion, renal vasoconstriction as a result of e.g. release of adenosine from malignant cells [2,16,17].

Hyperphosphataemia develops 24–48 hours after initiation of cytoreductive treatment. High concentration of calcium-phosphate product leads to the precipitation of its crystals in the renal collecting ducts and hypocalcaemia [16].

Prior to lysis, the main mechanisms of hyperkalaemia are: disrupted functioning of a sodium/potassium adenosine triphosphatase (ATPase) due to increased cellular consumption of adenosine triphosphate (ATP) in malignant cells exposed to chemotherapy or radiation, and after lysis, the release of potassium from stores of broken cells [17]. This electrolyte disturbance appears 6–72 hours following initiation of anticancer treatment [16].

Some authors indicate the possible role of hypercytokinaemia, which can cause systemic inflammatory response syndrome and multiple organ dysfunction syndrome [18-21].

Symptoms

TLS can be asymptomatic. Symptoms usually occur within 12 to 72 hours after initiation of cytoreductive therapy [1]. The clinical signs of TLS are presented in Table IV [1,16,22].

Diagnosis

An identification of patients at risk of TLS is essential [6]. Not only appropriate causal therapy should be given, but also urine output, fluid balance, serum levels of electrolytes, lactate dehydrogenase (LDH), creatinine and uric acid should be monitored in this group of patients. Duration of the monitoring period and its frequency depend on the patient condition and the therapeutic regimen [2].

Based on the Cairo-Bishop definition (Table V), TLS can be classified as laboratory tumor lysis syndrome (LTLS) or clinical tumor lysis syndrome (CTLS) [1,2]. The latest guidelines do not regard the calcium level as a criterion for establishing LTLS. A decrease in calcium level can be associated with high phosphate levels not being a direct consequence of TLS [6].

Management

The aims of TLS management is preservation of renal function, prevention of dysrhythmias and neuromuscular irritability [2]. TLS treatment principles are similar in hematological and solid tumors [8]. Aggressive hydration 2-3 L/m^2/per day is the main point of prevention and management of TLS [1]. If it is necessary and there are no contra-indications, loop diuretics can be used to sustain a urine output of 80-100 ml/m^2/hour [1,14]. They are essential to improve renal blood flow and glomerular filtration rate and to increase urine volume, dilution and excretion of metabolites [2]. Nephrotoxic agents (contrast media, selected antibiotics, non-steroidal anti-inflammatory drugs) and agents decreasing excretion of uric acid (aspirin, thiazide-type diuretics) should be

Table I
Differences in TLS between hematological malignancies and solid tumors [8].
Zespół rozpadu guza w nowotworach hematologicznych i guzach litych – porównanie [8].

Tumor type	hematological	solid
Frequency of occurrence	very high	very rare
Time of onset	early, even prior to anticancer therapy	may be late, even several days to weeks after anticancer treatment
Correlation with sensitivity of tumor to anticancer treatment	very high	variable
Mortality	low	high

Table II
Risk factors for TLS [10].
Czynniki ryzyka zespołu rozpadu guza [10].

Risk Factors for Tumor Lysis Syndrome
● Cancer type: mostly hematological malignancies but TLS can occur also in solid tumors, e.g. hepatocellular, colon, small cell lung carcinoma
● High rate of proliferation of cancer cells
● High sensitivity to anticancer therapy/ high intensity of treatment
● Bulky tumor
● Extensive metastases
● In case of solid tumors: liver metastases with/ without liver function abnormalities
● High level of lactate dehydrogenase (LDH)
● High level of white blood cells count (WBC)
● Dehydration or volume depletion
● Pre-existing renal insufficiency/ kidneys involvement at diagnosis
● Pre-existing hyperuricaemia
● Acidic urine promoting uric acid crystals precipitation
● Hypotension
● Exposure to nephrotoxins
● Underlying problems, e.g. infection

Table III.
TLS risk classification system [6].
Klasyfikacja grup ryzyka zespołu rozpadu guza [6].

LRD	IRD	HRD
● majority of solid tumors	● neuroblastoma, germ cell tumors, small cell lung cancer and others rare solid tumors with bulky or advanced stage disease and high sensitivity to chemotherapy	● no solid tumors
● multiple myeloma ● chronic myeloid leukaemia (CML) ● indolent non-Hodgkin lymphoma (NHL) or intermediate grade NHL in adults with LDH <2 * ULN ● Hodgkin lymphoma (HL) ● chronic lymphoid leukaemia (CLL) treated with alkylating agents ● acute myeloid leukaemia (AML) with WBC <25 * 109/L and LDH <2 * ULN ● anaplastic large cell lymphoma (ALCL) in adults	● AML with WBC 25-100 * 109/L or WBC <25 * 109/L and LDH ≥2 * ULN ● intermediate grade NHL in adults with LDH ≥2 * ULN ● ALCL stage III/IV in children, ● intermediate grade NHL stage III/IV in children with LDH <2 * ULN ● acute lymphoblastic leukaemia (ALL) with WBC <100 * 109/L and LDH <2 * ULN ● Burkitt lymphoma/ leukaemia with LDH <2 * ULN ● lymphoblastic lymphoma (LL) stage I/II with LDH <2 * ULN ● CLL treated with fludarabine, rituximab or with WBC ≥50 * 109/L	● AML with WBC ≥100 * 109/L ● ALL with WBC ≥100 * 109/L and/ or LDH ≥2 * ULN ● Burkitt lymphoma/ leukaemia stage III/IV and/ or LDH ≥2 * ULN ● LL stage III/IV and/ or LDH ≥2 * ULN

ULN - upper limit of normal

Table IV.
Symptoms of TLS [1,16,22].
Objawy zespołu rozpadu guza [1,16,22].

Hyperuricaemia	● nausea, vomiting, diarrhea, anorexia ● symptoms of renal insufficiency (e.g. oliguria, anuria, edema)
Hyperkalaemia	● diarrhea, vomiting, anorexia, weakness ● muscle cramps, paresthesia ● electrocardiographic changes (widening of the QRS complex and peaked T waves) ● cardiac arrhythmias, ventricular tachycardia, fibrillation, cardiac arrest
Hyperphosphataemia	● nausea, vomiting, diarrhea ● lethargy, seizures
Hypocalcaemia	● cardiac arrhythmias, hypotension ● tetany, muscular cramps

Table V.
Cairo-Bishop definition laboratory and clinical TLS [1,2].
Laboratoryjny i kliniczny zespół rozpadu guza – definicja według Cairo-Bishop [1,2].

LTLS (Laboratory Tumor Lysis Syndrome)	**Uric acid**	≥8 mg/dl (476 µmol/l) or 25% increase from baseline
	Potassium	≥6 mg/l (6 mmol/l) or 25% increase from baseline
	Phosphorus	≥4,5 mg/dl (1.5 mmol/l) for adults ≥6,5 mg/dl (2.1 mmol/l) for children or 25% increase from baseline
	Calcium	≤7 mg/dl (1.75 mmol/l) or 25% decrease from baseline
≥2 of the above, 3 days before to 7 days after the initiation of anticancer treatment are required		
CTLS (Clinical Tumor Lysis Syndrome)	renal insufficiency: creatinine >1.5 * ULN	
	cardiac arrhythmias or sudden death	
	Seizures	
The presence of LTLS and ≥1 of the above clinical complications are required		

ULN - upper limit of normal

avoided [11]. In the past, urinary alkalinization was one of the steps of hyperuricaemia management. It increases uric acid solubility (from 15 mg/dL in pH 5.0 to 200 mg/dL in pH 7.0) [1]. However, in alkaline urine, greater potential of precipitation of hypoxanthine and xanthine (usually elevated in patients treated with allopurinol) and calcium phosphate in renal tubules is observed [2,23,24]. Optimal treatments for preventing uric acid precipitation are uricolytic agents and improvement of urine flow. Alkalinization of urine is no longer recommended [1,24].

Uric acid lowering agents can preserve or improve renal function and reduce - as a second beneficial effect - the serum phosphorus levels [2]. The impact of these drugs on uric acid metabolism is presented in Figure 1. Uric acid is poorly soluble in water. In many species, there is an enzyme urate oxidase which converts uric acid into much more soluble allantoin. In humans it is not present.

Allopurinol is a xanthine analog which competitively blocks xanthine oxidase and thereby uric acid formation. It is ineffective in reducing pre-existing uric acid pool [2]. Allopurinol demonstrates efficacy in management of hyperuricaemia in patients at TLS risk but this drug can take several days until reductions in uric acid levels are observed [24]. An increase in the levels of xanthine and hypoxanthine and precipitation of their crystals in the renal tubules may occur after application of allopurinol**.** This agent also interferes with metabolism of other purine-based substances (e.g. 6-mercaptopurine, azathioprine) and methotrexate, decreasing their clearance. For that reason, lower doses of those drugs are required when used concomitantly with allopurinol. Combining allopurinol with capecitabine is contraindicated [1]. In patients with renal insufficiency, a 50% reduction of allopurinol is recommended. Allopurinol can cause hypersensitivity reactions, such as rash or fever [1,22].

Uricozyme is a nonrecombinant urate oxidase initially isolated from *Aspergillus flavus*. It promotes the catabolism of uric acid pool and causes a faster decrease in its serum level than allopurinol. During uric acid conversion into allantoin, H_2O_2 is released causing oxidative stress [1]. In glucose-6-phosphate dehydrogenase (G6PD) deficiency, the breakdown of H_2O_2 is ineffective and toxicities like hemolysis or methemoglobinaemia occur [24].

Rasburicase is a recombinant urate oxidase produced by the genetically modified *Saccharomyces cerevisiae*. It allows purification of the drug, potentially reducing the risk of contaminant-related hypersensitivity reactions [1]. As it has been shown in a randomized clinical trial, rasburicase is superior to allopurinol in reducing and controlling the plasma uric acid level [25]. Rasburicase has been approved to be administered at the daily dosage of 0.2 mg/kg for up to 5 days. Its

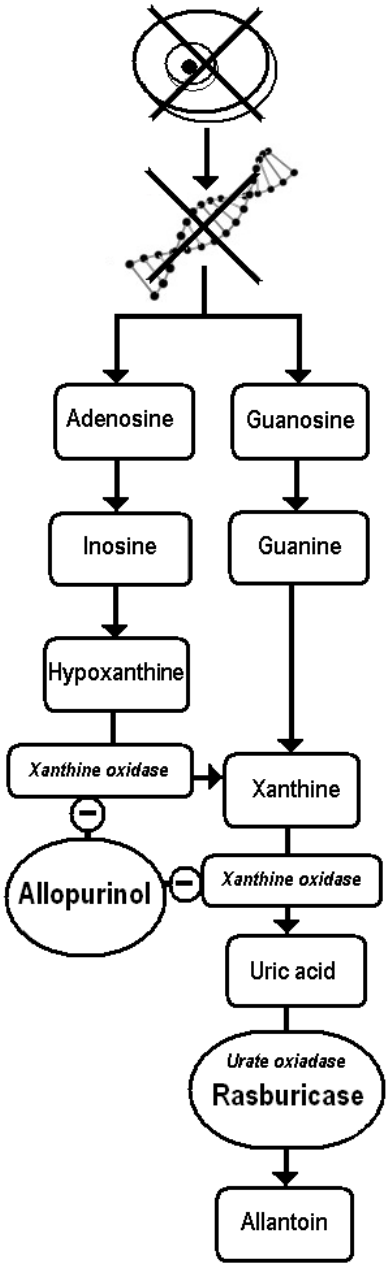

Figure 1.
Scheme of metabolism of nucleic acids from broken malignant cells and points of action of allopurinol and rasburicase [2].
Schemat metabolizmu kwasów nukleinowych uwalnianych z rozpadłych komórek nowotworowych i punkty uchwytu działania leków: allopurinolu i rasburykazy [2].

action occurs 4 hours after the first dose has been applied, and is effective in reducing the pre-existing uric acid pool, not causing hypoxanthine or xanthine accumulation [1]. The results of the randomized study showed that a single dose of rasburicase is effective in reducing and maintaining the uric acid level [26]. Using rasburicase, followed by allopurinol, can also effectively reduce the uric acid concentration and maintain it at a low level [25]. Known G6PD deficiency or history of hypersensitivity to urate oxidase are contraindications of using rasburicase [1]. Potential adverse reaction are: anaphylaxis, rash, hemolysis, methemoglobinaemia, fever, neutropaenia, respiratory distress, sepsis, mucositis, vomiting, diarrhea or headache**.** If rasburicase is contraindica-

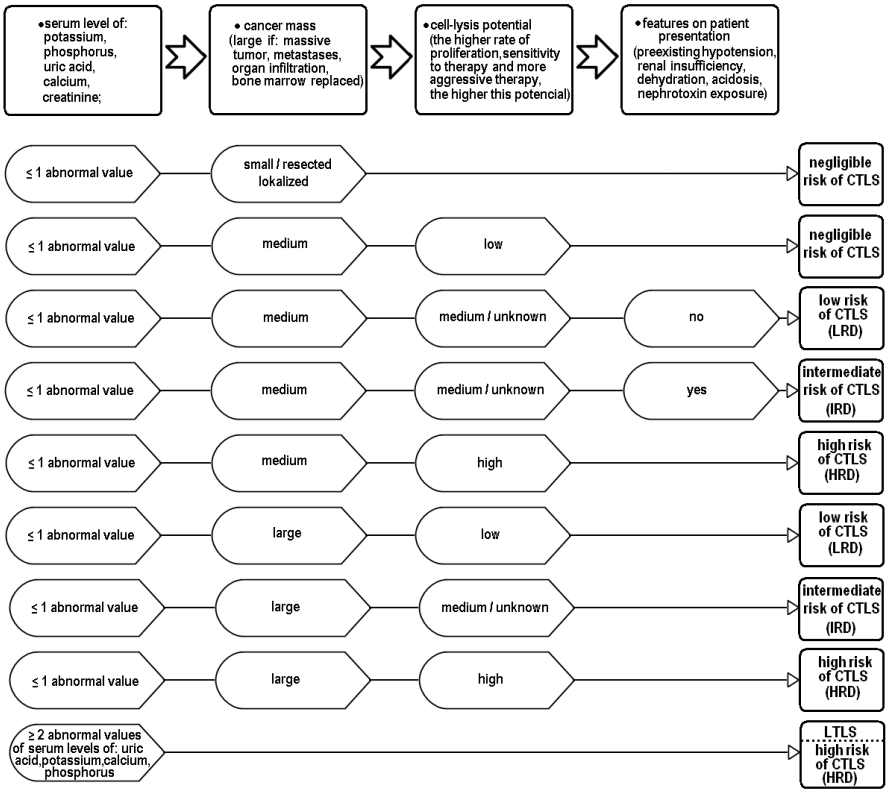

Figure 2
Algorithm of management of patients at TLS risk [2].
Algorytm postępowania u pacjentów z ryzykiem wystąpienia zespołu rozpadu guza [2].
„•" means „assessment of"; TLS – tumor lysis syndrome; LTLS – laboratory tumor lysis syndrome; CTLS – clinical tumor lysis syndrome; LRD – low risk of disease; IRD – intermediate risk of disease; HRD – high risk of disease.

Table VI.
Guidelines for TLS management [1,6].
Wytyczne postępowania w zespole rozpadu guza [1,6].

TLS risk	Action
Low	► monitor for development of TLS and complications ► normal hydration ► no prophylaxis for hyperuricaemia ► in the case of bulky, advanced or high proliferative disease or signs of metabolic abnormalities, add allopurinol ► in the case of LTLS use rasburicase
Intermediate	► monitor for development of TLS and complications ► increased hydration (3 L/m^2/d) ► allopurinol (100–300 mg, orally, q8h, daily) ► in adults with hyperuricaemia use rasburicase; in children consider rasburicase ► in the case of LTLS, use rasburicase
High	► monitor frequently for development of TLS and complications ► increased hydration (3 L/m^2/d), unless evidence of renal insufficiency and oliguria ► rasburicase (0,1–0,2 mg/kg), one dose repeated only if clinically necessary

ted, allopurinol should be used. Due to the high costs of rasburicase, it is essential to monitor the serum uric acid level to adjust the optimal duration of treatment [23]. Blood samples must be immediately placed on ice until the completion of assay because rasburicase degrades uric acid *ex vivo* at room temperature [23].

An appropriate conventional management should be introduced for prevention and treatment of electrolytes abnormalities. It is essential to treat symptomatic hypocalcaemia**.** Care must be taken to avoid increased concentration of the calcium-phosphate product and its potential precipitation in the kidney and other tissues [2].

The latest recommendations for management of TLS included in Table V are based on the risk classification system presented in Table II [1,6]. In daily clinical practice**,** an algorithm of care based on actual patient condition seems to be more applicative (Figure 2). The assessment of TLS risk is based on a clinical judgment of actual patient's features and easily defined tumor characteristics. It is more universal as it is not based on tumor histology [2]. Prevention and treatment options in each risk group are similar to those presented in Table VI. In the case of low urine output, persistent or elevated potassium or phosphate levels and hypocalcaemia, a consultation with a nephrologist and dialysotherapy should be considered [1]. HRD patients should receive intensive nursing care in a facility with ready access to dialysis, continuous cardiac monitoring and laboratory monitoring every 4 to 6 hours. IRD patients should undergo laboratory monitoring every 8 to 12 hours, in case of LRD – once daily [1,2]. If TLS has not developed within 2 days after finishing chemotherapy, the likelihood of its occurrence is minimal [1,2]. Generally, it is recommended to hold up with anticancer treatment since the prevention measures have started to act. Usually, the delay varies from 24 to 48 hours. In aggressive tumors, it is possible to administer rasburicase and start chemotherapy with only a few hours' delay [27]. Patients who have a high risk of TLS may receive low-intensity initial therapy. It causes slower tumor lysis and allows the kidneys to clear metabolites more effectively [2].

Summary

TLS is an oncological emergency. Abrupt lysis of malignant cells and release of intracellular contents into the systemic circulation can cause life-threatening metabolic and electrolyte disturbances. The prophylaxis is a cornerstone in TLS management. The lysis of tumor cells can develop as a result of anticancer treatment or may occur spontaneously. TLS affects bulky tumors with a high proliferative rate and sensitivity to chemotherapy. It is the most common of all hematologic malignancies but it can also occur in solid tumors. Patients are divided into low, intermediate and high risk groups, based on tumor type, stage and patient presentation. Different prevention and treatment options have been elaborated in this article. Knowledge about actual guidelines is essential to introduce the most appropriate management of TLS in particular groups of patients.

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