Acute Tumor Lysis Syndrome: A Metabolic Emergency in Cancer Patients

Giorgio Attinà[1], Raffaele Tepedino[2] and Antonio Ruggiero[1]*

[1]Pediatric Oncology Unit, Fondazione Policlinico Universitario A.
Gemelli IRCCS, Universita' Cattolica Sacro Cuore, Rome, Italy.
[2]Medicine and Surgey Faculty. Università La Sapienza, Rome, Italy.
*Corresponding Author E-mail: antonio.ruggiero@unicatt.it

Tumor lysis syndrome (TLS) can be a life-threatening complication that occurs following the onset of chemotherapy treatment, most commonly in association with high-grade lymphoproliferative pathologies such as acute lymphoblastic leukemia and Burkitt lymphoma. The massive cell lysis caused by cytotoxic therapy leads to the rapid release in the blood of intracelullary products and the onset of severe metabolic and electrolytic complications (hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia) upto the acute renal failure. This article describes the incidence and pathophysiological basis of TLS, focusing on the new therapeutic strategies implemented over the last few years, especially with regard to the treatment of hyperuricemia. In particular, it highlights the characteristics of a recent drug, Rasburicase, as a safe and effective alternative, compared to traditional allopurinol therapy, for prophylaxis and treatment of children with hyperuricemia induced by chemotherapy.

Keywords: Allopurinol; Hyperuricemia; Rasburicase; Tumor Lysis Syndrome.

Acute Tumor Lysis Syndrome (TLS) is a metabolic and electrolytic disorder due to a rapid increase in the blood of intracellular products, originating from massive lysis of cancer cells following the beginning of cytotoxic therapy. The release of intracellular products determines hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia with metabolic consequences on the normal homeostatic mechanisms, up to the acute renal failure [1]. Therefore, TLS is a potentially lethal complication of chemotherapy, which requires proper prophylaxis and adequate treatment.

Epidemiology

TLS is commonly associated with high-grade lymphoprolifeative diseases particularly frequent in children, such as acute lymphoblastic leukemia and Burkitt lymphoma[1]. It can be also a complication of chronic lymphatic leukemia, acute myeloid leukemia, multiple myeloma, and isolated plasmacytoma.

Some cases are reported in the course of other haematological disorders, such as non-Hodgkin lymphomas, Hodgkin lymphomas, chronic myeloid leukemia (in the phase of blastic crisis) and myeloproliferative disorders. TLS has

been rarely observed in solid tumors characterized by a high degree of proliferation and high response to cytotoxic therapy, such as testicular cancer, breast cancer, and pulmonary microcytoma.

Physiopathology
Hyperkalemia

Hyperkalemia is the result of massive potassium release into the extracellular space because of cellular lysis. It can occur from 6 to 72 hours from the beginning of chemotherapy[2].

Some concomitant conditions such as acute renal failure, chronic renal disease, acidosis, or excessive iatrogenic administration of potassium during the induction phase of chemotherapy may contribute to exacerbating such electrolyte imbalance.

Clinical symptoms commonly include nausea, vomiting, diarrhea, and anorexia. In presence of severe hyperkalemia (>7 mmol/l) neuromuscular signs and symptoms may also appear, such as cramps, weakness, paresthesias, paralysis, and cardiovascular alterations, such as arrhythmias (tachycardia or ventricular fibrillation), electrocardiographic alterations (loosening of the QRS complex and pointed T-wave), syncope, and sudden death [3-7].

Hyperphosphatemia

Hyperphosphatemia can occur between 24 and 48 hours from the start of chemotherapy and can cause nausea, vomiting, diarrhea, lethargy, and seizures[2].

The evidence that cancer cells may contain up to 4 times more organic and inorganic phosphorus than non-malignant cells[8] favours its onset. In addition, acute renal insufficiency, particularly when associated with uric acid precipitation or other complications induced by chemotherapy, may contribute to a significant exacerbation of this imbalance[9,10].

Hypocalcemia

Hypocalcemia is generally due to precipitation of calcium phosphate crystals into the renal tubule because of hyperphosphatemia[8].

When the calcium-phosphorus product exceeds a value of 70, the risk of deposition of calcium phosphate at the level of the kidney and other organs becomes particularly high[8,11,12], resulting in metastatic calcifications. In particular, at the renal level it is possible to find clinical conditions ranging from the nephrocalcinosis to the nephrolithiasis up to the acute obstructive uropathy[3,4].

Hypocalcemia can lead to several complications: 1) musclular: cramps, spasms, paresthesias, and tetanus; 2) cardiovascular: ventricular arrhythmias, cardiac arrest, and hypotension; 3) neurological: confusion, delirium, hallucinations, and convulsions.

In addition, severe hypocalcemia can also lead to severe clinical manifestations, such as heart failure, coma and, rarely, death[3-5, 13-15].

Hyperuricemia

Hyperuricemia is the result of the rapid catabolism of intracellular nucleic acids released following the lysis of cancer cells and occurs, in general, between 48 and 72 hours from the beginning of therapy[2,16,17].

In TLS, hyperuricemia is severe, as the tumor cells have increased replicative activity and, therefore, a greater amount of nucleic acids.

Uric acid has a pKa of 5.4-5.7 and is slightly soluble in water. Its clearance occurs at the renal level and normally a quantity of 500 mg/day is excreted. At normal concentration and physiological pH, more than 99% of uric acid is present in ionised form[13]. In the presence of acidic pH and a high concentration, however, uric acid precipitates at the tubular level in the form of crystals, resulting in obstruction, development of acute obstructive uropathy and renal dysfunction[3,4].

Obstructive uropathy is responsible for several clinical manifestations, such as hematuria, flank pain, hypertension, hyperazotemia, acidosis, edema, oliguria, anuria, lethargy, and drowsiness[4,5].

Uremia

Uremia is a clinical syndrome that follows the acute renal failure caused by metabolic and electrolytic alterations of the TLS. It is a multifactorial process that recognizes different causes, such as the formation and deposition of uric acid crystals into the renal tubules, the deposition of calcium phosphate crystals and/or xanthine crystals, the tumor infiltration of the kidney, ureteral obstruction, the use of nephrotoxic drugs, and acute sepsis [8,18-20].

The clinical manifestations are related to the renal failure and include nausea, vomiting, oliguria, anuria, edema, hypertension, congestive heart failure, metabolic disorders, exacerbation of hyperphosphatemia and hyperkalemia, severe

hematuria and acidosis, up to the impairment of the state of consciousness with confusion, drowsiness, lethargy, convulsions, and coma[3,4,5].

Risk Factors

TLS risk factors belong to two categories: a) pre-existing risk factors such as reduced urinary flow, pre-existing hyperuricemia, dehydration, low urinary pH, and kidney failure[8,19]; b) tumour-related risk factors, including tumour volume, proliferative rate, kidney tumor infiltration, chemotherapy sensitivity, and LDH level[1,21].

Prevention and treatment
Preventive strategies

The implementation of strategies to prevent and/or reduce the severity of clinical manifestations of the TLS plays a crucial role. Patients at high risk of developing TLS or suffering from TLS, during the first 48-72 hours of chemotherapy, should be subjected to close monitoring of the following laboratory parameters: the assessment, every 4-6 hours, of serum electrolyte levels, of uric acid, creatinine and urea nitrogen, could allow a rapid correction of electrolyte disorders, reducing the risk of fatal complications. It would also be appropriate to correct hypovolemia if present, avoid the administration of nephrotoxic drugs and agents able to block the tubular reabsorption of uric acid.

These measures are accompanied by other important prophylactic and therapeutic measures described below.

Hyperhydration

Hydration is recommended for all patients at risk of TLS : the decrease of serum concentration of uric acid, phosphate and potassium and the increase of urinary flow, with reduced concentration of solutes in the renal tubules, decrease the formation and precipitation of the crystals of urate and calcium phosphate[22-26].

Hydration should start immediately following the patient's admittance to the ward and continued up to 2-3 days after chemotherapy. It is important that the fluids reserved for hydration do not contain potassium, calcium and phosphate[3,4,27].

Patients should receive hyperhydration of at least 3 l/m^2/day (200 ml/kg/day in children up to a weigh of 10 kg) and maintain a urinary flow of 100 ml/m^2/hour (3 ml/kg/hour in children up to a weight of 10 kg), with a specific urine weight at d"1,010.

In patients without acute obstructive uropathy and/or hypovolemia, diuretics may also be required (mannitol with a dose of 0,5mg/kg or furosemide with a dose of 0,5-1 mg/kg)[27-30].

Alkalinization of urine

Alkalinization of urine has been recommended for prevention and/or treatment by TLS, based on the evidence that alkaline urine facilitates the excretion of uric acid released during TLS. However, nowdays the use of this practice is controversial for two reasons:

1. alkaline urinary pH promotes precipitation of calcium phosphate at the renal level and other organs, increasing the risk of renal insufficiency;

2. alkalinization also significantly reduces the solubility of xanthine, facilitating the formation and precipitation of xanthine crystals, with consequent increased risk of kidney failure.

Hyperkalemia

Based on the serum potassium level, 2 therapeutic approaches are suggested:

• Asymptomatic and moderate hyperkalemia (e" 6 mmol/l): avoid the administration of potassium, both intravenously and orally; monitor the patient through the execution of ECG control. The treatment includes the administration of sodium sulfonate polystyrene (1g/kg with sorbitol 50%) for oral administration or endorectally. However, not having an immediate effect, should not be used in patients with severe arrhythmia;

• Symptomatic and/or severe hyperkalemia (> 7 mmol/l): administer calcium gluconate (100-200 mg/kg iv) and/or regular insulin (0,1 U/kg iv) + dextrose 25% (2 ml/kg iv)[25,31].

Calcium gluconate allows stabilization of the heart cell membrane, preventing arrhythmias and, due to its short half-life, should be repeated at the need. Insulin, on the other hand, promotes the transition of potassium from the extra-to the intracellular space and is administered together with dextrose to prevent a hypoglycemic status[5,32].

Sodium bicarbonate might also be used as, in addition to having a mechanism of action similar to insulin, corrects metabolic acidosis. In patients with kidney damage should be administered cautiously for the risk of inappropriate volume expansion. More aggressive treatments, such as dialysis, are performed in patients with acute renal failure[22,33].

Hyperphosphatemia

Hyperphosphatemia is defined by phosphorus values of e"2,1 mmol/l in children and e" 1,45 mmol/l in adults.

In presence of moderate hyperphosphatemia it is important not to infuse phosphate iv and the treatment of choice provides for the administration of phosphorus chelating agents, such as aluminum hydroxide, which can be taken through nasogastric tube feeding at a dose of 15 ml every 6 hours (50-150 mg/kg/24 h). If phosphorus chelating agents do not control hyperphosphatemia, it can be necessary to utilize more aggressive treatments, such as peritoneal dialysis, hemodialysis or continuous veno-venous haemofiltration. Some authors have pointed out that phosphorus clearance is significantly better as a result of haemodialysis (9.8 mg/min) than continuous venous haematofiltration (1 mg/min) and peritoneal dialysis (0.3 mg/min)[4,34-40].

Hypocalcemia

Hypocalcemia is a metabolic disorder related to hyperphosphatemia causing the tissue precipitation of calcium phosphate. Hypocalcemia is defined as a total serum calcium concentration < 8.8 mg/dL (< 2.20 mmol/L) in the presence of normal plasma protein concentrations or as a serum ionized calcium concentration < 4.7 mg/dL (< 1.17 mmol/L).

No treatment is recommended for asymptomatic hypocalcemia. Following the appearance of the first symptoms, however, the patient must be treated with calcium gluconate, with a dose of 50-100 mg/kg iv. This treatment, however, could increase the risk of calcium phosphate deposition, resulting in acute obstructive uropathy[4].

Hyperuricemia

Hyperuricemia (defined for uric acid values e"480 ìmol/l) is an important risk factor for the formation and precipitation of urate crystals in the renal tubules. Therefore, it is fundamental that adequate hydration is performed. Serum levels of uric acid can also be reduced by inhibiting its formation, obtained by allopurinol, or by increasing its renal clearance by treatment with Rasburicase.

Allopurinol is an analogue of xanthine which prevents the formation of uric acid through the inhibition of xanthine oxidase (Fig.1)[41-43].

Therefore, the formation of new uric acid decreases and reduces the risk of obstructive uropathy[41,31].

It's been available in oral form since 1966 and in intravenous form in the United States since 1999. The recommemded dose level is 200-400 mg/m²/day in adult patients and 200 mg/m²/day in children, divided in 1-3 doses, up to a maximum dose of 600 mg/day.

This type of treatment has important limitations:
• Slow start of action; the reduction of serum uric acid levels in patients in allopurinol therapy occurs after 2-3 days;
• While preventing the new formation of uric acid, it does not reduce the levels of uric acid pre-existing at the beginning of therapy;
• The dose should be reduced in patients with renal damage since oxypurinol remains active for 18-30 hours and being eliminated by the renal route may have a substantially increased half-life in patients with renal insufficiency[5,22];
• Leads to an increase in the precursors of uric acid, xanthine and hypoxanthin, favouring the development of urinary crystals and acute obstructive uropathy[42, 44-46];
• Increases the medullary toxicity of cyclophosphamide and reduces the degradation of 6-mercaptopurine and azathioprine. Therefore, during the concomitant treatment with allopurinol, it is recommended to reduce the dose of these drugs, in particular 6-mercaptopurine, by 50-70%. Allopurinol also interferes with the pharmacokinetics of other drugs, such as dicumarol, cyclosporine, and thiazide diuretics;
• 3% of patients develop hypersensitivity reactions to this drug, and in some patients a severe allergic reaction has also been described, such as Steven-Johnson syndrome.

An alternative therapeutic strategy to allopurinol involves the use of agents that, instead of inhibiting the formation of uric acid, facilitate kidney clearance, through conversion to more soluble products mediated by the urate oxidase.

In 1975 it was introduced in Europe as a prophylactic treatment of TLS, the oxidase urate not recombinant, an enzyme isolated from Aspergillus flavus and proved effective in reducing serum levels of uric acid[47-53].

Its use has, however, been limited by the high risk of anaphylaxis that the drug involved,

although the introduction of glycolpolyethylene has reduced the incidence[50, 54].

For this reason, a form of recombinant oxidase urate has recently been developed, Rasburicase. It is an enzyme produced from a genetically modified strain of Saccharomyces cerevisiae, the use of which was approved in Europe in 2001.

Rasburicase catalyzes enzymatic oxidation of uric acid to allantoin, a product which, at the urinary level, is 5-10 times more soluble than uric acid (Fig. 1)[55,56].

Being a recombinant enzyme, it has a higher degree of purity, therefore higher specificity (> 50% compared to the native enzyme) and greater tolerability.

Rasburicase should be administered immediately before and during the starting of chemotherapy. The recommended dose is 0.2 mg/kg/day. It is administered once a day by intravenous infusion of 30 minutes in 50 ml of 0.9% sodium chloride solution. The duration of treatment can vary between 5 and 7 days. However, recent studies have shown that low doses (0.05-0.20 mg/kg) and/or short-term treatments (1-3 days) could have the same efficacy of the dose and the original schedule, allowing, a better cost-benefit ratio through reduced costs and exposure to Rasburicase[57-62].

Rasburicase has a half-life of 19 hours and a clearance of about 3.5 ml/ kg/h. Its metabolism occurs by peptide hydrolysis, so liver failure does not influence the pharmacokinetics and in patients with renal insufficiency it is not necessary to reduce the dosage[57,58].

In addition, in a randomized phase III study, the efficacy of Rasburicase (0.20 mg/kg/day administered iv) vs allopurinol (300 mg/m^2/day for os in 3 doses) was compared in 52 pediatric patients with leukemia or lymphoma. The two-hypouricemizing agents were administered
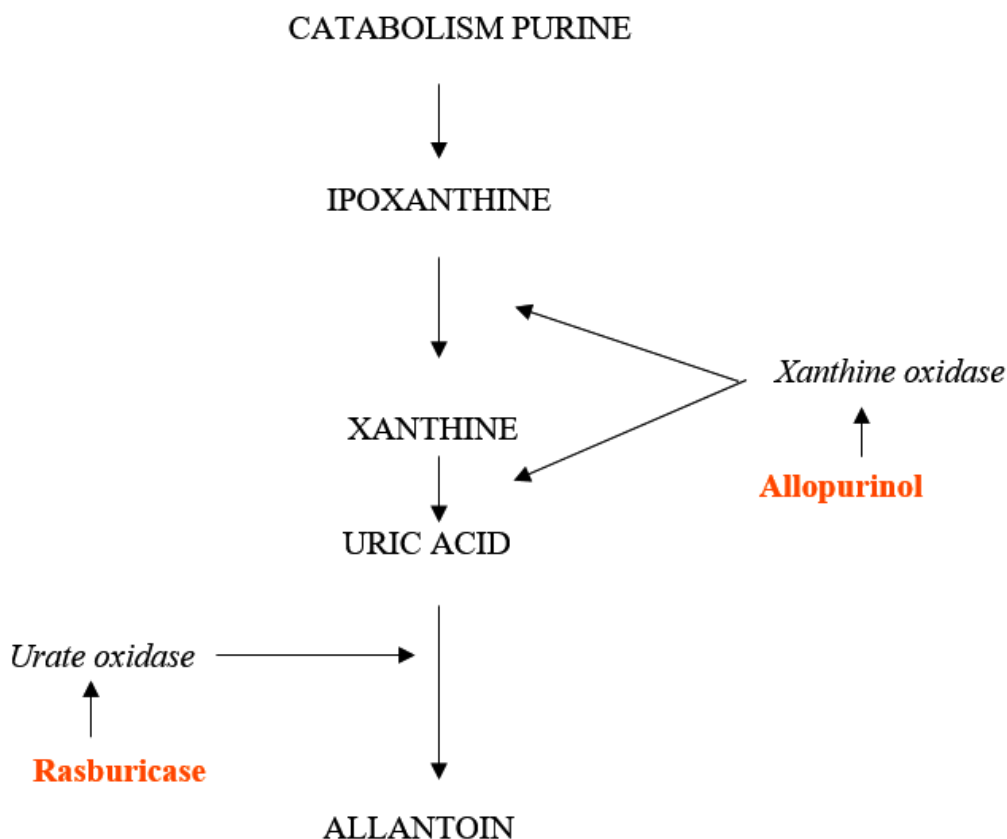

Fig. 1. Metabolic process of purines

randomly during chemotherapy. It has been observed that, compared to allopurinol, Rasburicase has a greater effectiveness in the treatment of hyperuricemia (p<0,0001) and has a faster mechanism of action. In fact, after 4 hours from the first dose, plasmatic uric acid levels were reduced by 86% in patients treated with Rasburicase and by 12% in those treated with allopurinol (p<0,0001) (31). Sample size was too small to be able to determine a difference in the incidence of kidney failure. In the allopurinol-treated group, a 12-year-old patient with adavanced Burkitt lymphoma needed hemodialysis during the study period, while in the group treated with Rasburicase it has been documented that a 15-year-old patient with renal baseline insufficiency improved the renal conditions during the therapy, without the need for dialysis or haematofiltration. For a better evaluation of the relationship between renal function and treatment, were also analyzed levels of creatinine in hyperuricemic patients during the first 96 hours of therapy.

Patients treated with Rasburicase showed at baseline a creatinine value of 144% compared to the average defined by age/sex and following the first 4 days decreased to 102%; in the group treated with allopurinol, however, the values have worsened from 132% to 147%. Therefore, Rasburicase when compared to allopurinol allows not only a faster and more efficient control of uric acid levels, but also an important improvement of renal function. For this reason, alkalinization of urine is currently being discussed in patients undergoing this type of treatment, especially in relation to the complications it entails[63].

Finally, we recall that treatment with Rasburicase can cause fever, nausea, vomiting; diarrhea, and headache. Allergic side effects were also described, mainly rashes, bronchospasm (<1%) and severe hypersensitivity reactions, including anaphylaxis (<1%). In addition, in patients with glucose-6-phosphate dehydrogenase deficiency and with non-hereditary hemolytic anemia this drug is contraindicated, leading to an increased risk of hemolytic anemia or metahemoglobinemia[57,64-71].

Uremia and acute renal failure

The treatment of renal insufficiency associated with acute TLS requires a careful monitoring of fluids introduced, the control of hypertension, the correction of electrolytic alterations and the reduction of the dosage of drugs normally excreted by the renal route.

Sometimes, the response to the medical therapy is poor and it is necessary to adopt aggressive treatments, such as hemodialysis, peritoneal dialysis or continuous veno-venous haemofiltration. For uric acid clearance, the best results were reported by haemodialysis patients (70-145 ml/min) compared to those who performed peritoneal dialysis (15 ml/min) and continuous veno- venous haemafiltration (6,2 ml/min)[4].

CONCLUSIONS

TLS is a serious metabolic and electrolytic disorder that occurs during chemotherapy, resulting from the lysis of cancer cells. It is characterized by the presence of hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia and can lead to acute renal failure. Therefore, the identification of patients at risk, the development of preventive strategies, the careful monitoring and the adequate correction of clinical and laboratory parameters play a crucial role, allowing to reducing the risk of fatal complications. In particular, hyperuricemia should be carefully treated adopting appropriate hydration and medical therapies such as allopurinol or rasburicase favouring the uric acid clearance and reducing the incidence of nephropathy.

Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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