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TUMOR LYSIS SYNDROME: PATHOGENESIS AND CLINICAL ASPECTS

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Tumor lysis syndrome (TLS) is a life-threatening metabolic emergency that occurs as a result of spontaneous-or, more frequently- treatment related cancer cell death. Biochemical abnormalities can be ascribed to the rapid destruction of tumor cells with subsequent massive and synchronized release of cellular breakdown products, that overwhelm excretory mechanisms and the body's capacity to reutilize these products.[1] Four cardinal signs can be recognized: hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia.

Hyperkalemia

Potassium is an intracellular ion whose gradient across cell membrane is maintained by an ATP-dependant pump. Early events leading to cell apoptosis induce a decrease in ATP levels and subsequent leakage of potassium out of intact tumor cell membrane. Hyperkalemia is the earliest abnormality of TLS, being observed at 12-24 hours after the start of chemotherapy, as it occurs prior to complete cell lysis.

Hyperphosphatemia and hypocalcemia

Spontaneus or chemo-therapy induced DNA fragmentation leads to the release of a great amount of nucleotides and phosphate, whose concentration is frequently higher in tumor cells as compared to their normal counterpart.[2] Initially the kidneys respond to the increased concentration of phosphorous by increasing urinary excretion and decreasing tubular reabsorption, however, when the mechanisms become saturated, a rise in phosphorous levels is observed, usually 24-48 hours after the start of chemotherapy. Hyperphosphatemia leads in turn to hypocalcemia due to precipitation of calcium phosphate,[3] that results in tissue calcification and nephrocalcinosis. Low serum calcium levels induce an increased secretion of parathyroid hormone which causes a decreases reabsorption of phosphate by proximal tubule, thus contributing to the maintainance of the vicious circle.

Hyperuricemia

Tumor cell lysis releases a great amount of pyrimidine and purine nucleotides. Pyrimidines are degraded into their constituents and subsequently reutilised; purines undergo a complex series of biochemical reactions (Figure 1) leading to the formation of uric acid.

Mammals other than man can oxidate uric acid into allantoin by urate oxidase; in humans, on the contrary, the kidneys have to manage a great uric acid load. Uric acid is 13 times more soluble at pH 7.0 than at pH 5.0;4 this metabolite is freely filtered at the glomerulus, partially reabsorbed at proximal tubule and secreted at distal tubule, where precipitation may be favored by ongoing tubular acidification. The presence of calcium phosphate crystals can further contribute to uric acid precipitation in distal tubules.

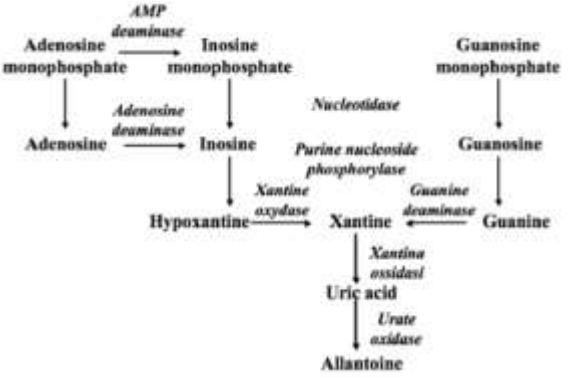

Figure 1. Purine degradation pathway.

Clinical findings

The clinical picture of TLS is carachterized the complex series of disturbances caused the single metabolic abnormalities. Specifically, hypekalemia is responsible for paresthesias, muscle weakness and, above all, cardiac signs (QRS widening, bradycardia, ventricular arrhythmia) that can result into syncope and sudden death. Hypophosphatemia and, in particular, hypocalcemia, can cause cardiac arrhythmias, muscle cramps, tetany, and seizure, potentially leading to coma. Hyperuricemia is the main cause of acute renal failure (uric acid nephropathy), that frequently represents the major clinical finding in TLS. Several factors can further contribute to the development of acute renal failure, namely hyperleukocytosis with consequent decreased renal perfusion and acidosis; renal infiltration by tumor cells; abextrinseco obstruction; fever, with consequent dehydration; use of nephrotoxic antibiotics; nephocalcinosis due to deposition of calcium-phosphate crystals.

Incidence and risk factors

In a retrospective study of 102 patients with high-grade non Hodgkin's lymphoma, overall incidence of TLS has been reported to be 42% with 6% of the patients experiencing clinically relevant symptoms.[5] This complication is very fequent in the pediatric setting; almost 25% of the children with advanced-stage Burkitt's lymphoma or B-cell acute lymphoblastic leukaemia experience acute renal failure at onset of cytoreductive chemotherapy.[6-7]

Risk factors can be classified as patient-related, tumor-related and therapy related. Patients at risk of developing TLS are those with a pre-existent alteration of renal function, hyperuricemia or dehydration. With respect to tumors, TLS occurs more frequently in the presence of bulky abdominal involvement, hyperleucocytosis, rapidly proliferating neoplasms and elevated serum lactate dehydrogenase (LDH),[8] the latter being related to tumor growth fraction. Specifically, TLS is more frequently observed in individuals affected by haematological malignancies such as Burkitt's lymphoma,[9] B-cell and T-cell non Hodkgin's lymphomas and acute lymphoblastic leukaemia, but may also occur in patients with acute myeloid leukaemia and blastic phase of chronic myeloid leukaemia. TLS may also be observed in the presence of solid tumors such as smll cell lung cancer, breast car-

cinoma, neuroblastoma, metastatic seminoma and soft tissue sarcoma.[10-11] As to concern cytotoxic therapy, corticosteroids have been most frequently implicated in the pathogenesis of TLS especially as they are employed as primary therapy of highly-proliferating lymphoid disorders.[12] The whole spectrum of metabolic disturbances, however, has been also described in association with many compounds (fludarabine, rituximab, radiation therapy, bortezomib, tamoxifen and alfa-interferon) some of which are known for their mild cytotoxic activity, so that the combined effect of tumor sensitivity and drug specificity must be considered responsible for the occurrence of TLS in these settings.

In conclusion, TLS is a serious metabolic disorder that can lead to patients death or can severely impair the opportunity of the patients to receive an adequate therapy for their neoplasm; for these reasons it is mandatory to promptly recognize and treat TLS and, when possible, to prevent its onset.

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NEPHROLOGICAL COMPLICATIONS OF TUMOR LYSIS SYNDROME

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Introduction

Acute Tumor Lysis Syndrome is characterized by a set of metabolic complications that usually occur after the treatment of neoplastic disorders. The findings that may be observed include besides hyperuricemia, electrolyte abnormalities (hyperphosphatemia, hyperkaliemia, hypocalcemia) and acute renal failure. The syndrome was first reported in 1929[1] in patients with chronic leukaemia. Since this original description the presentation of the syndrome has changed. The introduction of allopurinol, and to a lesser extent uricase, before the onset of anti-tumor therapy has reduced, but not eliminated, the incidence of acute uric acid nephropathy. Nowadays, acute renal failure following therapy is more frequently associated with severe hyperphosphatemia. Moreover, spontaneous acute renal failure prior to therapy is now more commonly recognized and is usually due to acute uric acid nephropathy. These patients have an increased uric acid production and hyperuricosuria due to the high rate of tumor cell turnover. A retrospective study performed in four European countries has shown that the incidence of tumor lysis syndrome was 6% in patients with non-Hodgkin's lymphoma, while 1.9% of the global population observed died as result of TLS-related complications.[2] In this series, tumor lysis syndrome led to acute renal failure in 45% of the patients, with the need for renal replacement therapy in half of the patients.

Uric acid, phosphate, potassium and calcium metabolism

The massive breakdown of large quantities of intracellular nucleic acids resulting from the lysis of large number of tumor cells can produce high uric acid concentrations that facilitate crystallization in the collecting ducts and in the deep cortical and medullary vessels, causing a reduction in the urine flux. Hyperphosphatemia, very common after chemotherapy, contributes along with calcium phosphate deposition, to the damage in the tubular and interstitium system. An important distinction between spontaneous tumor lysis and the one occurring after therapy is the lack of hyperphosphatemia in the spontaneous form. On the contrary, DNA fragmentation in rapidly dividing cells by chemotherapy or massive steroid therapy only results in the release of degenerated nuclear material, including nucleotides and phosphate. In most cases the severity of hyperphosphatemia is aggravated by a reduction in the glomerular filtration rate. Hyperphosphatemia is usually followed by the decrease in the serum calcium, which leads to secondary hyperparathyroidism and an aggravation in the already elevated phosphorus and calcium phosphate product. Calcium phosphate precipitation in the renal tubules may lead to acute renal failure. Hyperphosphatemia may also aggravate acute renal failure when pre-existent to tumor lysis. As demonstrated in rats by Zager,[3] phosphate infusion prior to the induction of ARF leads to vacuolization of the proximal tubular cells and to glomerular capillary collapse. It has been postulated that rapidly growing neoplasias with high cell turnover rates can lead to high uric acid levels through a rapid nucleoprotein turnover, but that the tumor is able to reutilize released phosphorus for re-synthesis of the new tumor cells. In contrast, the acute increase in uric acid levels associated with chemotherapy is due to cell destruction; in this setting, there are no new cancer cells to reutilize the large amounts of released phosphorus. The enhanced relative importance of hyperphosphatemia in rela-

tion to hyperuricemia can be illustrated by the findings in two reports. One study evaluated 33 patients either with Burkitt's lymphoma or undifferentiated lymphoblastic lymphoma [3]. The following observations were made: 61 per cent of patients developed at least a two-fold increase in urinary phosphate excretion following the initiation of therapy. Forty-five per cent developed significant hyperphosphatemia (greater than 5.0 mg/dL) with peak values seen two to four days after treatment. Hyperuricemia (greater than 8.0 mg/dL) was seen in 21 percent but did not exceed 10.6 mg/dL in any patient. Five patients developed acute renal failure with the plasma phosphate concentration ranging from 6.4 to 9.5 mg/dL. LDH levels were used as a marker for the degree of tumor lysis. Seven of 13 azotemic patients increased their LDH levels 30 per cent or more above the pre-treatment level, a finding seen in only two of 19 non-azotemic patients. High LDH levels prior to therapy were predictive of azotemia, hyperuricemia, and hyperphosphatemia after therapy. A later study reviewed the incidence of tumor lysis syndrome in 102 patients with non-Hodgkin's lymphoma (intermediate to high grade histology) who received aggressive combination chemotherapy and allopurinol prophylaxis.[4] Laboratory abnormalities developed in 42 percent of the patients studied and were more common in those with pre-treatment azotemia: the plasma phosphate concentration rose by more than 25 percent in one-third of cases and was above 8 mg/dL in nine. Four patients with hyperphosphatemia developed acute renal failure. Significant hypocalcemia (plasma calcium concentration less than 8 mg/dL developed in eight patients and severe hypocalcemia (plasma calcium concentration less than 6 mg/dL in two. Despite allopurinol, plasma uric acid levels rose by more than 25 percent in 28 patients (27 percent). The uric acid concentration exceeded 15 mg/dL in three patients, one of whom developed acute renal failure. The plasma potassium concentration was greater than 5.5 mEq/L in four patients who had renal insufficiency. To this proposal we must point out that hyperkalemia is the most life–threatening manifestation of the syndrome. It is caused by potassium efflux from lysed tumor cells and is exacerbated by acute renal failure and metabolic acidosis.

Acute nephropathy

Acute nephropathy is the consequence of the exposure of uric acid crystals in the distal tubules, the collecting ducts, the renal pelvis or the ureter causing an intra or extrarenal outflow obstruction and renal failure. Factors predisposing to the development of acute uric acid nephropathy are an: increased urinary acid concentration, extracellular volume depletion, concentrate urine and acid urinary pH. Contributing factors are high rates of cell turnover, exquisite sensitivity to chemotherapy as in Burkitt's lymphoma and steroids and FANS therapy. Other factors contributing to the acute renal failure may be hypotension and exposure to nephrotoxic agents, such as antimicrobial agents, chemotherapy and contrast media. Patients with malignancies are often depleted owing to poor oral intake, vomiting, diarrhoea, and insensible losses from fever or tachipnea. Two different pathogenetic mechanisms with different clinical presentation may be involved. One disease presenting with acute onset of hyperuricemia may lead to the diffuse intrarenal deposition of uric acid in the distal tubule and collecting duct where maximal acidification and concentration contribute to uric acid precipitation. This is most typical in the tumor lysis syndrome provoked by chemotherapy and seldom provokes abdominal pain and oligoanuria. On the other hand, a more insidious disease may lead to a more prolonged period of moderate hyperuricosuria, causing the formation of multiple uric acid stones with ureteral or pelvis obstruction. In this type of acute uric acid nephropathy, which is now rarely encountered, hyperuricemia tends to be less severe, but colicky irradiating flank pain is typical.

Diagnosis

The tumor lysis syndrome should be suspected in patients with a large tumor burden who develop acute renal failure in the presence of marked hyperuricemia (greater than 15 mg/dL) and/or hyperphosphatemia (greater than 8 mg/dL). These levels are in contrast to most other forms of acute renal failure in which the plasma uric acid concentration is less than 12 mg/dL and the plasma phosphate level is less than 6 mg/dL. One exception is pre-renal disease in which hyperuricemia is induced by the increases in proximal sodium and urate reabsorption. Acute uric acid nephropathy is almost always oligoanuric. It is typically associated with no symptoms referable to the urinary tract, although flank pain can occur if there is renal pelvic or ureteral obstruction. Hypocalcemia is usually asymptomatic, but can cause neuromuscular irritability and tetany. The urinalysis may show many uric acid crystals or amorphous urates in an acid urine, but can occasionally be relatively normal due to lack of output from the obstructed nephrons. Over-excretion of uric acid can be documented in many patients by a urine uric acid-to-creatinine ratio (mg/mg) above 1.0 on a random urine specimen; by comparison, the value is below 0.60 to 0.75 in most other forms of acute renal failure. Patients developing spontaneous TLS have an advanced tumor stages with a large tumor burden, refracted by markedly raised serum LDH levels.

Treatment

Effective management of the tumor lysis syndrome is a combination of prophylaxis, prevention, and appropriate dialysis treatment.

- *Prophylaxis.* The major goals of preventing lysis syndrome, in any patient who might develop it, are to keep serum potassium, uric acid , and phosphate levels within normal limits and to maintain high urinary flow. Patients about to receive chemotherapy or radiation for a malignancy with rapid cell turnover should be pre-treated for at least two days with allopurinol (in higher than normal doses of 600 to 900 mg/day) plus fluid loading (with saline and possibly mannitol) to maintain a high urine output (greater than 2.5 L/day). An alternative agent for the management of hyperuricemia is rasburicase, a recombinant form of urate oxidase isolated as a complementary DNA clone from *Aspergillus flavus*, expressed in the yeast strain *Saccharomyces cerevisiae*. Reversible forms of renal insufficiency (volume contraction, hypercalcemia, urinary tract obstruction) should be corrected prior to therapy. The role of urinary alkalinization with acetazolamide and sodium bicarbonate is less clear. Alkalinization will convert uric acid to the more soluble urate salt, thereby diminishing the tendency to uric acid precipitation. However, experimental studies suggest that hydration with saline alone is as effective as alkalinization in minimizing uric acid precipitation. Furthermore, alkalinization has the potential disadvantage of promoting calcium phosphate deposition in patients with marked hyperphosphatemia and is therefore not recommended.

- *Acute uric acid nephropathy prior to chemotherapy.* Therapy after the onset of acute renal failure consists of allopurinol (if it has not already been given) and attempting to wash out the obstructing uric acid crystals with a loop diuretic and fluids. An alternative agent for the management of hyperuricemia is rasburicase, a recombinant form of urate oxidase isolated as a complementary DNA clone from Aspergillus flavus, expressed in the yeast strain Saccha-

romyces cerevisiae. The rasburicase is a powerful urycolitic agent and its toxicity profile is excellent showing a rare incidence of bronchospasm and allergies. In a setting of nine patients with renal failure and elevated uric acid levels we evaluated the behaviour of uric acid and the activity of urate oxidase after the administration of a single dose of rasburicase (0.20 mg /Kg i.v.) (Figure 1).

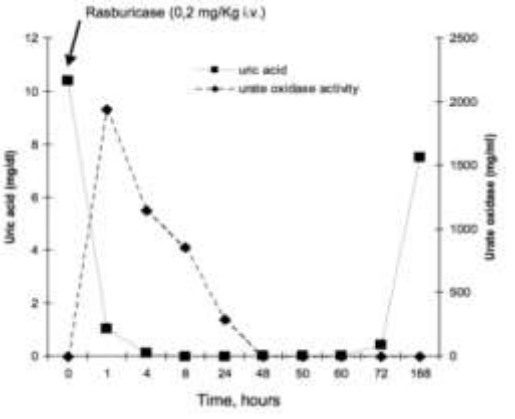

Figure 1. Trends of uric acid levels and plasma urate oxidase concentration after the administration of single dose of rasburicase.

One dose of rasburicase induced a rapid and sustained therapeutic effect of lowering the plasma uric acid levels in all patients. Moreover, the activity of the enzyme seems to finish after 48 hours, with the level of uric acid remaining low in all the patients (Figure 2).

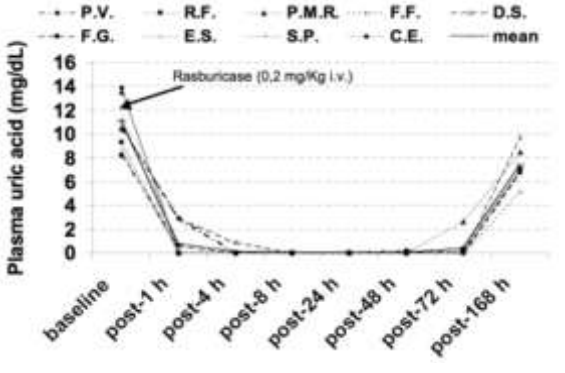

Figure 2. Individuals plasma levels of uric acid concentration after a single dose of rasburicase in nine patients with hyperuricemia and different degrees of renal failure.

Hemodialysis to remove the excess circulating uric acid should be used in those patients in whom a diuresis cannot be induced. The prognosis for complete recovery is excellent if treatment is started rapidly. Studies have shown that oliguria due to acute uric acid nephropathy responds rapidly to hemodialysis with the start of a diuresis as the plasma uric acid level falls to 10 mg/dL.[6] Hemodialysis is very efficient in removing uric acid; uric acid clearance is approximately 70 to 100 mL/min and the plasma uric acid level falls by about 50 percent with each 6-hour treatment. Peritoneal dialysis is much less efficient with clearances below 10 mL/min.

- *Acute renal failure following chemotherapy.* Hyperkalemia management involves protection against the arrythmogenic action of increased potassium levels with the intravenous administration of calcium gluconate, intracellular potassium shift with the administration of insulin and glucose, and the correction of metabolic acidosis with the use of bicarbonate. If the high potassium levels persist and the patient is symptomatic, hemodialysis will correct hyperkalemia and other concurrent metabolic abnormalities, even when there is no concomitant renal failure. As noted above, marked hyperphosphatemia is usually the precipitating factor in this setting. The rapid recovery of renal function in the oligoanuric patient requires the normalization of phosphorus and uric acid levels (allopurinol and rasburicase).Volume expansion with isotonic saline increases renal blood flow, glomerular filtration rate, and urine volume leading to decreased concentrations of solutes in renal tubules and making precipitation less likely. Phosphate binders, such as aluminium antacids, calcium carbonate, sevelamer will decrease the gut absorption of phosphate. Hemodialysis should be considered in the case of persisting anuria. Depending on the dialyzer and blood flow, phosphorus clearance usually ranges between 60 and 100 mL/min with hemodialysis. The phosphate burden in these patients can vary from two to seven grams per day; as a result, it is frequently necessary to perform hemodialysis at 12- to 24-hour intervals. Continuous arteriovenous hemodialysis (CAVHD) with a high dialysate flow rate and continuous veno-venous hemofiltration may also be effective. The phosphorus clearance with CAVHD, for example, can reach 40 mL/min at a dialysate flow rate of four litres per hour. This can lead to the removal of up to 10 grams of phosphorus per day without the rebound hyperphosphatemia often seen after intermittent hemodialysis.[7]

Conclusions

Tumor lysis syndrome is seen most frequently in patients with lymphoprolipherative disorders, but also in those with solid tumors. The syndrome is most often seen after chemotherapy, which leads to massive cells death and lysis of cell contents: the rapid destruction of tumor cells leads to hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia and acute renal failure. The pathophysiological process results from the precipitation of uric acid in the tubules and the development of obstruction to filtration. The metabolic and electrolyte derangements of tumor lysis syndrome may be concurrently exacerbated by renal failure and may be fatal. High awareness is required especially in patients with sensitive tumor types and well-known pre-treatment risk factors, such as renal impairment, hyperuricemia, and increased lactate dehydrogenase. Early recognition and appropriate treatment should decrease the fatal complications of the syndrome.

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TIENTS WITH HAEMATOLOGICAL MALIGNANCIES

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A massive lysis of tumor cells, due to rapid cellular turnover by themselves or to chemotherapy, with release of cellular breakdown products such as uric acid, can cause severe hypeuricemia (HU).[1] This occurs commonly in tumors with a high proliferative rate, a relative large tumor burden and high sensitivity to chemotherapeutic drugs (i.e. acute lymphoid or myeloid leukemia (ALL, AML) or Burkitt's lymphoma, etc.).[2,3] A combination of two or more metabolic disturbance including HU, hyperphosphatemia, hyperkaliemia and hypocalcemia is referred to as tumor lysis syndrome (TLS). This latter can lead to life-treating complications such as severe hyperkaliemia resulting in cardiac arrhythmia, neurological complication and acute renal failure (ARF) due to precipitation of uric acid crystals and calcium phosphate in the renal tubules.[4] Therefore, according to the presence/absence of these life-treateing complications TLS should be classified as laboratory TLS (LTLS) or clinical TLS (CTLS). In an attempt to provide a unified definition with clinical relevance Cairo and Bishop recently proposed a new grading classification of TLS in which patients were divided into five groups.[5] The first group had no evidence of either laboratory and/or clinical TLS at the time of presentation whereas the other four groups had a LTLS associated with the presence of one or more of the three most significant clinical complications associated with TLS: renal insufficiency, cardiac arrhythmias/sudden death and seizures.[5]

In adult patients with haematological malignancies, a hyperuricemic condition (>8mg/ml) was reported in a percentage of cases variable from the 11% reported by Coiffier *et al.,*[6] in 100 NHL to the 62% reported by Jeha *et al.,*[7] in a group of 387 patients presenting a higher heterogeneity as for diagnosis. Moreover, a previous retrospective study of 102 patients with NHL reported an incidence of LTLS in 42% of cases while the incidence of clinical relevant was only 6%.[8] However, TLS has been reported more commonly in acute lymphoid leukaemia (ALL) and in high grade NHL, in particular Burkitt's Lymphoma. Other haematological malignancies, that have been less commonly associated with TLS include chronic lymphocytic leukaemia, acute myeloid leukaemia, and plasma cell disorders including multiple mieloma and isolated plasmacytomas.[5,9]

Clinical manifestation of TLS may include nausea, vomiting, lethargia, cramps, tetany, paresthesias, paralysis, syncope, seizures, cardiac dysrhythmias and sudden deaths. These symptoms may have their onset prior to initiation of therapy but more commonly they can occur within 12-24 h after administration of chemotherapy. Therefore, the key to the management of TLS is prevention. Thus, it is essential to immediately identify patients at high risk of developing TLS and to aggressively institute a proactive prophylactic strategy to prevent and/or reduce the severity of clinical manifestation of acute TLS. To this purpose, the first group of Cairo and Bishop grading classification of TLS has been further broken down into two distinct sub-group categories, according to their risk of developing TLS. The low risk group included patients with non-haematological malignancies, low tumor burden, low chemosensitivity, low white blood cell (WBC) count and/or low lactate dehydrogenase (LDH) levels. By contrast, the high risk group included patients with haematological malignancies with a high proliferative rate (i.e. Burkitt's lymphoma, lymphoblastic lymphoma, etc.), high tumor burden, high WBC count, hyperuricemia, high LDH levels and/or high chemosensitivity. In high risk patients, tumor therapy should be delayed, if possible, until prophylactic measures can be initiated.[5]

Since acute HU it has been recognized as the principle responsible of anuria and uremia, the mainstay goals of current prophylaxis are to decrease uric acid production and increase its excretion by the kidney. The necessity of hyper hydration (3 L/m^2) to maintain high urine output was proposed as the principal effective preventive measure. In this way it is possible to improve intravascular volume, enhance renal blood flow and glomerular filtration and promote urinary excretion of uric acid and phosphate. Urine alkalinization (pH>7) has historically been general recommendation for the prevention and/or treatment of TLS, because alkaline urines promote the urinary excretion of urate. However, the use of sodium bicarbonate to alkalinise the urine is became debated due to the fact that alkalinization and allopurinol therapy may increase the formation of urinary xantine crystals and, more importantly, it may favour the precipitation of calcium phosphate. Allopurinol is a structural analogue of the purine base hypoxantine. By inhibiting the enzyme xantine oxidase, allopurinol blocks uric acid formation. Several studies suggested that allopurinolo is effective in preventing the formation of future uric acid, but will not affect the removal of the existing uric acid load.[9] Consequently, a drug that has a rapid and highly potent uricolytic properties, reduce metabolic morbidity, and can be convienently integrated with the initiation of a cancer chemotherapy regimen would be helpful in the supportive management of this patient population. Urate oxidase catalyzes the enzymztic oxidation of uric acid into allantoin, a readily excretable substance about 5 times more soluble than uric acid. Urate oxidase is an endogenous enzyme found in most mammals, but not in humans because of a non sense mutation in the coding gene in the gene during huminoid evolution.[10] Rasburicase is a recombinant form of the urate oxidase enzyme.[11] A study in healthy adult male volunteers establisheed that single daily intraveneous doses of rasburicase were well tolerated and led to dramatic decreases in plasma uric acid levels. A recent multicenter phase II trial of rasburicase in pediatric patients with leukemia and lymphoma demonstrated that 100% of patients achieved uric acid control at a dose of rasburicase of 0.2 mg/kg despite intensive chemotherapy. The approved dosage of rasburicase is 0.15-0.2 kg i.v. once daily for five days, with chemotherapy initiation recommended 4-24 hours after the initial dose. Recently, Jeha *et al.,*[7] explored the utility of Rasburicase in 245 patients (173 children and 72 adults). All patients entered this study had a hematologic malignancies and were hyperuricemic or at high risk for this complication. In this study patients were grouped in the prophylaxis group, if their baseline serum uric acid (SUA) levels were within the normal range, or in the treatment group if their SUA levels were above the normal values. The response to Rasburicase was excellent. In fact, either in children or in adults and in normouricemic or in hyperuricemic patients, the authors demonstrated a significant reduction of the median SUA levels that persisted very low despite the subsequent administration of chemotherapy.

These results were further confirmed by Coiffier *et al.,*[6] that reported the control of SUA values within 4 hours after the first administration of the drugs. Moreover, in this study, creatinina levels and other metabolities were also controlled by rasburicase. To date, only one trial has randomly compared allopurinol and rasburicase in patients at high risk of acute TLS. Findings of this study showed that rasburicase significantly reduced the exposure to uric acid and area

under the curve for mean uric acid 0-96 h (AUC 0-96) for patients with hyperuricemia compared with allopurinol (12). Despite the clinical advantages of rasburicase over allopurinol, the cost of rasburicase plays an important role in the management of hyperuricemia. To date, there is only one published pharmaeconomic analysis, that showed that rasburicase, in addition to the demonstrated clinical benefit, is an economically attractive new option in the treatment of HU, both in adults and in children, whereas in prevention the drug has an attractive economic profile in children, and is cost-effective in adults with ALL and NHL.[12] However, in an effort to reduce costs and exposure to rasburicase, recent studies have demonstrated that doses lower than the 0.15-0.20 mg/kg and/or short treatment duration of 1-3 days may be as effective as the original dose and schedule and may be more cost effective.[13]

In conclusion, the above considerations recommend to prevent and/or treat HU. Patients considered to have no LTLS or CTLS with low risk of developing TLS would be candidates for allopurinol prophylaxis. By contrast, patients with either the presence of LTLS and/or CTLS would be better candidates for rasburicase prophylaxis and therapy of HU. However, the following issues still deserve to be better clarified: 1) which subgroup of patients are at the highest risk of developing TLS; 2) which dose or schedule of rasburicase is most effective for both prophylaxis and treatment, 3) can rasburicase and allopurinol can be used sequentially for prophylaxis and treatment; and 4) does rasburicase reduce morbidity and mortality from TLS.

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TUMOR LYSIS SYNDROME: PREVENTION AND TREATMENT THERAPEUTIC GUIDE LINES AIEOP

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Introduction

Hyperuricemia and tumor lysis syndrome (TLS) are complications that can arise from treatment of rapidly proliferating and drug-sensitive neoplasms. We investigated the safety and efficacy of rasburicase in the AIEOP centers experience with the aim to propose written TLS Guidelines for pediatric patients. TLS is a constellation of metabolic abnormalities that results from the rapid death of tumor cell and release of their contents into the circulation. Malignant cell death is mostly associated with cytoreductive therapy appearing usually 12-72 h from the start. The classic triad of TLS includes hyperuricemia, hyperkalemia and hyperphosphatemia that can be associated with hypocalcemia. TLS arise more frequently in children with tumor's high proliferative fraction, large burden or wide dissemination and high chemo-sensitivity which are described in Table 1.

Table 1. Risk factors for TLS.

Hyperleukocytosis
Large tumor burden
High LDH
Elevated uric acid
Massive organ enlargement
Chemosensitive tumors
Pre-existing renal dysfunction

In a recent paper Wossmann *et al.,*[s] analyzed the incidence and complications of TLS in 1791 children with non-Hodgkin lymphoma (NHL) enrolled in the two subsequent multicenter studies NHL-BFM 90 and 95. Out of this group 78 (4.4%) developed a TLS and 42 (2.3%) oligoanuria. Patients with Burkitt's lymphoma or B-ALL had a higher incidence of TLS (8.4%) and anuria (4.4%); in particular patients with B-ALL had the highest risk to develop a TLS (26.4%) and anuria (14.1%). Of the 790 patients with Burkitt's lymphoma or B-ALL, tumor burden as indicated by the plasma level of LDH was the main predictor for the development of both TLS and anuria. The TLS incidence was 1.2, 12.7, 19.1% for patients with LDH level <500, 500-1,000, >1,000 U/liter respectively. The incidence of TLS in patients with T-lymphoblastic lymphoma and other B-cell NHL was below 2% and anuria occurred in less 1%. TLS has also been documented in childhood solid tumors such as neuroblastoma and medulloblastoma and it is rare in acute myeloid leukemia (AML) despite the high blood cell count.[2] As more active chemotherapeutic regimens and immunotherapies become available for the management of cancer, previously untreatable malignancies are becoming highly responsive to treatment and subject to the same precautions seen with the highly proliferate hematopoietic diseases. TLS has also been observed, although rarely, in children treated with agents that do not have a potent cytotoxic action such as interferon-α, interleukin-2, STI-571, intrathecal methotrexate and other various drug therapies, such as corticosteroids, fludarabine, as well as radiation in preparative regimens for bone marrow transplantation. In the pediatric literature there are a few case reports of children who present hyperuricemia and acute renal failure as an initial presentation of occult lymphoproliferative disorder.[3]

Therapy and Prophylaxis of Tumor Lysis Syndrome

The goal of therapy is to implement preventive treatment regimens and, once evident, to correct the metabolic abnormalities immediately. Close monitoring for risk factors, immediate identification and intervention are essential in preventing the life-threatening consequences of TLS. Prophylactic measures had considerably decreased the incidence of TLS and the morbidity associated. The standard prophylaxis of TLS and urate nephropathy consists of hidration, alkalinization, allopurinol and cytoreductive prophase. For most patients this regime suffices to prevent clinically significant TLS and acute renal failure (ARF). Hydration is the most important aspect of the management and prevention of TLS. Aggressive hydration (2.5-3 liters/m^2/day) should start at least 24 h before chemotherapy. Most clinicians felt that urine alkalinization is mandatory because uric acid is more soluble at high pH (>7), so precipitation of uric acid in renal tubules would thereby be avoided. However, there is no scientific proof in the literature that this approach is effective: a study done in 1977 showed that alkalinization did not improve the abnormalities induced by hyperuricemia.[4] Furthermore, in the presence of hyperphosphatemia and hypocalcemia, the use of alkalinization might aggravate manifestations of hypocalcemia and increase the risk for calcium-phosphate deposition in the kidneys. Allopurinol (300 mg/m^2/day), by preventing the conversion of hypoxanthine and xanthine to uric acid, has long been long considered the standard pharmacological approach to hyperuricemia and prevention of TLS. However, allopurinol itself may facilitate precipitation of xanthine crystals, has little influence on already-formed uric acid crystals deposited in the kidney and it may take several days for uric acid levels UAL to normalize. Laboratory evaluation of patients at high risk of developing TLS involves frequent clinical laboratory testing (every 12 h for at least 3 days) including complete blood count, serum sodium, potassium, chloride, calcium, phosphorus, uric acid, BUN, creatinine (in specific cases creatinine clearance (Ccr by Schwartz formula or cystatin C) and urinalysis. It is recommended that a nephrologist be consulted at the first sign of TLS for management of any early involvement. Exogenous potassium source, ACE inhibitors, potassium-sparing diuretics, and drugs known to interfere with aldosterone should be avoided. In some cases a conventional management would be unable to prevent metabolic instability and ARF. An alternative approach to managing severe hyperuricemia included the administration of Uricozyme,® a non-recombinant urate-oxidase present in many different organisms, but not in the higher primates, which converts uric acid to allantoine, a readily excretable metabolite five to ten times more soluble at normal tubular pH. Rasburicase, an urate-oxidase recombinant form produced by a genetically modified strain of *Saccharomyces cerevisiae* expressing cDNA cloned from a strain of *Aspergillus flavus*, available in Europe, Australia and USA over the last 2 years, has been defined as a well tolerated and potent urolytic agent for the treatment and prophylaxis of malignancy-associated acute hyperuricemia, and also in order to prevent renal failure.[5] Rasburicase has been reported to be significantly more effective than allopurinol in lowering UAL in patients at high risk of TLS. Pui *et al.,*[6] and Goldman *et al.,*[7] compared the use of urate oxidase with standard allopurinol and alkalinization in children with leukemia and Burkitt's lymphoma confirming the ability of urate oxidase to decrease the UAL faster and more reliably than has been shown for allopurinol. From three prospective studies, Goldman *et al.,*[8] also reviewed the safety and efficacy of rasburicase to both treat and prevent hyperuricemia in 246 chil-

dren with acute leukemia and NHL at risk for TLS which showed substantial reduction in UAL with an excellent efficacy/toxicity ratio in both groups of patients. A schedule of rasburicase at a dose of 0.2 mg/kg given intravenously once daily for 5-7 days has been recommended in patients at risk of TLS, but successful treatment with shorter duration of use has also been reported.[9]

TLS and acute renal failure (ARF)

ARF can result from urate, xanthine or calcium phosphate kidney precipitation as well as from tumor involvement in the kidney. As reported by Stapleton *et al.,*[10] ARF continues to be a major in children with advanced stage of Burkitt's lymphoma and B-ALL. Ten years later, Seidemann *et al.,*[11] by a retrospective analysis of 1192 patients registered in the NHL-BFM trials, confirmed that, in pediatric NHL-patients, Burkitt's lymphoma and B-ALL appear to be the commonest cause of metabolic complications early in chemotherapy. In particular patients with an advanced stage and large tumor mass (92% LDH>500 U/L) and signs of impaired renal function at admission (69%) are at high risk for renal failure. In pediatric literature, there are several case reports suggesting that urate oxidase could be helpful to avoid dialysis in patients with hematological malignancies who develop TLS with ARF. Using Uricozyme, the French pediatric NHL group reported a very low incidence of dialyses (1.7%) during induction chemotherapy for Burkitt's lymphoma or B-ALL [12]. Finally, a steady improvement of renal function was seen during rasburicase prophylaxis for children with leukemia/lymphoma in a study reported by Pui *et al.,*[13]: renal function was within the normal range in all patients by day 6 of treatment and none required dialyses.

Experience of Associazione Italiana Ematologia Oncologia Pediatrica

In a recent study conducted by some Centers of Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), the efficacy of rasburicase, Fasturtec is reported, in reducing plasma UAL in children with malignancies at risk for developing TLS and who are submitted to treatment or prophylaxis of acute hyperuricemia. We retrospectively reviewed 26 patients (15 males, 11 females) who had been submitted to treatment or prophylaxis of malignancy-associated hyperuricemia from January to September 2003. Baseline characteristics of the patients are shown in Table 2.

Table 2. Patient characteristics.

Total	26	
Sex (M/F)	15/11	
Age median (range)	7 (1-18)	
Malignancies		
- ALL	11 (42%)	
- NHL	8 (31%)	
- AML	4 (15.5%)	
- Solid tumor	3 (11.5%)	
Groups	**Hyperuricemic**	**Non-hyperuricemic**
Cases	12 (46%)	14 (54%)
UAL (mg/dL)	13.73 ± 3.42	3.98 ± 1.68
Creatinine (mg/dL)	1.23 ± 0.52	0.52 ± 0.15
Azotemia (g/liter)	0.80 ± 0.30	0.24 ± 0.08
Phosphorus (mg/dL)	5.6 ± 1.53	4.6 ± 0.75

Rasburicase was given daily at 0.15-0.20 mg/kg intravenously in 50 mL normal saline solution over 30 min. The drug was administered in 19 patients (73%) at the first induction chemotherapy, starting 0-48 hours before the initiation of antiblastic infusion concomitantly, in 10 cases and in 7 patients (27%) during the chemotherapy treatment. The response to treatment was defined as maintenance or reduction of UAL ≤6.5 mg/dL at 48 h post-treatment and control of hyperuricemia under treatment. Response to the first dose was defined as maintenance or reduction of UAL with respect to the basal value at 24 after the start of treatment. A supplementary daily dose was indicated for patients at an especially high risk for hyperuricemia or uncontrolled UAL in the first 72 h. At presentation no patients showed significant history of atopy or G6PD deficiency. UAL was measured at the clinical laboratories before drug administration and then daily until at least 48 h after the last dose of rasburicase. Handling procedures and temperature conditions were observed during blood collection in all cases. Physical examination, complete blood counts, serum chemistries were performed daily. None of the patients had received previous treatment with Uricozyme® or Rasburicase.

Patients who were hyperuricemic at presentation were analyzed separately from those who were not hyperuricemic. Comparison of pre- and post-treatment UAL was computed with paired t-test. Descriptive summary statistics (N, mean, median, SD) were computed for each group.

The primary end-point of our study was to test the efficacy of rasburicase in controlling acute hyperuricemia during the induction or consolidation chemotherapy appropriate for the specific disease. All patients submitted to treatment or prophylaxis with rasburicase showed a highly significant (p<0.001) decline of UAL, maintained 48 h after the last dose. The mean UAL±SD after treatment was 0.71±0.64 mg/dL for *group 1*, and 1.18±1.14 mg/dL for *group 2*. The response rate was 100% for both groups. Uric acid concentrations remained low during the entire course of treatment, with a median and a maximum values not exceeding 2.84 mg/dL and 6.40 mg/dL, respectively, on any day. Only a 5-months-old non-hyperuricemic child (presenting UAL: 4.6 mg/dL), affected by AML, had a transient increase in UAL (from 0.10 mg/dL at 24 h to 6.4 mg/dL at 48 h), decreasing to 0.10 mg/dL 72 h after the first dose, showing, however, a good response to treatment. The second objective of our study was to test the rapidity of the control of UAL after a single dose of rasburicase. The urate-oxidase produced a rapid and significant (p<0.001) decrease in UAL within 24 h after the first injection in all our patients, except for a non-hyperuricemic patient at presentation (non-responder at the first dose). After the first dose the mean UAL ± SD was 0.51±0.39 mg/dL in *group 1*, and 1.83 ± 1.07 mg/dL in *group 2*, with a response rate of 100 and 92.9% for *groups 1* and *2*, respectively. One patient, a 13 year old girl affected by NHL, submitted to prophylaxis of acute hyperuricemia (presenting UAL: 5 mg/dL), had an increase of UAL 24 hours after the first dose (UAL_1: 5.8 mg/dL), decreasing to 5 mg/dL 4 days after the start of treatment, anyway showing a response, even tough not significant. The decline in UAL was more evident for the hyperuricemic patients. The median (range) treatment duration was 4 (1-11) days. No patients needed supplementary treatment to control UAL. Four of 5 patients (all from the group 1) with elevated serum creatinine levels at presentation (mean ± SD:1.86±0.47 mg/dL) showed a progressive decrease in creatinine concentrations from the 3rd day onwards with completely normal values 5 days after the start of treatment (mean ± SD:0.85±0.13 mg/dL) and did not develop renal failure or hypertension or require dialysis. A six-year-old girl, affected by Wilm's tumor, developed ARF with progressively increasing serum creatinine levels, which was then corrected by pharmacological treatment only. The 3 patients (all from the group 1) with elevated serum phosphorus concentrations at the onset (mean ± SD:7.8±0.48 mg/dL) had a decrease in phosphorus hematic levels with completely normal values 4 days after

the start of treatment (mean ± SD:3.7±0.46 mg/dL). Serum potassium and calcium concentrations were relatively stable throughout the treatment course in all cases. Rasburicase was very well tolerated in all our patients. In all cases the treatment with urate-oxidase was associated with hyperhydration (2-3 liters/m^2 daily), and in 19 cases (73%) with urine alkalinization. Our data demonstrate that rasburicase is a safe and highly effective drug for the prevention and treatment of hyperuricemia, with a marked decline in UAL 24 h after the first injection. The time over which the control of UAL occurs has not been evaluated in this limited set of patients, however, studies on both adults [14] and children [15] have demonstrated that UAL is reduced to normal values within 4 h after the first injection in the majority of the patients. In our study, patients presenting with hyperuricemia showed a greater response to treatment than non-hyperuricemic patients at baseline. Considering the duration of treatment, even if literature advises a mean number of 4 doses to control acute hyperuricemia in children [6], our study suggests that, in some patients, even hyperuricemic, with normal renal function, one dose could be sufficient. This confirms the need of individualizing treatment schedule according to the patient's clinical characteristics such as the type and the burden of malignancy, the anticancer treatment and, hence, the duration of tumor cell lysis. The steady improvement of renal function during treatment with urate-oxidase in the patients with impaired renal function at presentation, none of whom required dialysis, is remarkable in considering literature data. Hyperphosphatemia with consequent hyper-phosphaturia is another important cause of ARF due to tumor cell lysis. Rasburicase may obviate the need of urine alkalinization, facilitating phosphorus excretion. The last consideration cannot be analyzed in our study considering that only 27% of our patients did not receive sodium bicarbonate infusion. As with other oxidative agents, rasburicase should not be used in patients with known G6PDH deficiency. Hydrogen peroxide, one of the by-products of break-down of uric acid to allantoin, can induce hemolytic anemia or methemoglobinemia in patients with G6PDH deficiency. The pharmacoeconomics of rasburicase and its administration should be considered too. In this study we have not evaluated the pharmacoeconomic benefits or collected treatment-related costs. In conclusion Rasburicase is a safe and highly effective agent for the prevention and treatment of acute hyperuricemia, in particular, in the patients at high risk for developing TLS.

Table 3. Criteria to define the risk for TLS in children with malignancies.

High Risk		Low Risk
at least one of the following clinical and/or laboratory criteria		
Clinical criteria	Laboratory criteria	
ALL with leukemia/ lymphoma syndrome	WBC ≥50.000 m^3	
B ALL-FAB L3	UAL ≥7 mg/dL	No High
Stage III and IV NHL	LDH ≥2 times over the normal range	
Bulky disease	Phosphoremia ≥6.5 mg/dL	
Renal impairment at diagnosis	Creatinine or Ccr over the normal range for age	

Recommendations for TLS Prevention and Treatment in Children

On the basis of our experience and literature data we could advance some recommendations regarding the optimal use of human recombinant urate-oxidase in children defining risk stratification for developing TLS (Table 3).

Precocious identification of patients at high risk to develop TLS is critical. To define children at high risk of TLS, one of the following clinical or laboratory criteria is needed and sufficient:

Clinical criteria:

-1 ALL with leukemia/lymphoma syndrome: the presence of mediastinal enlargement or lymph-node involvement or high WBC count plus T immunophenotype or normal Hb level or normal platelet counts are criteria to recognize this clinical profile at high risk for chemosensitivity and large tumorburden.

- 2 B ALL FAB L3: B mature ALL is constantly associated with FAB L3 (vacuolated cells) category characterized by high chemosensitivity.
- 3 NHL stage III and IV: high tumor cell death, both spontaneous and chemotherapy induced, are present in advanced NHL stages.
- 4 Bulky disease: all cases with lymphoproliferative disorder with the presence of a large mass at onset have to be considered as high risk for TLS.
- 6 Renal impairment at diagnosis: apart from renal function failure, the involvement of kidneys in children at the onset represent a rare but relevant risk factor.

Laboratory criteria:

- 1 WBC ≥50,000/m^3
- 2 LDH ≥2 times over normal range
- 3 UAL ≥7 mg/dL
- 4 Phosphoremia ≥6.5 mg/dL
- 5 Creatininemia or Ccr (cm ≥0.55/creatinemia) over normal range for age

The remaining population is at low risk to develop TLS.

Patients at high risk of TLS will receive rasburicase (0.20 mg/kg/day) for 5 days in addition to hyper-hydration (2.5-3 liters/m^2 G5% plus electrolytes). Instead, patients at low risk, will be treated with the standard therapy: allopurinol (300 mg/m^2) in addition to hyper-hydration (2.5-3 liters/m^2 G5% plus electrolytes) and urine alkalinization (pH >7).

Regarding the use of rasburicase, we recommend the start of treatment at the dosage of 0.2 mg/kg/day just before (4 h) beginning chemotherapy and then continuing for as long as tumor lysis persists for duration of at least 4 days under chemotherapy. The elevated urinary allantoin excretion during the first 4 days of treatment, which reflects an ongoing generation of uric acid from tumor lysis, supports the need to continue rasburicase treatment for this duration: shorter treatment duration might increase the risk of failure. However, a single dose of rasburicase would be taken into account for the treatment of patients at low risk of TLS.

In patients at high risk of TLS levels of LDH, uric acid, sodium, potassium, creatinine, BUN, phosphorus and calcium would be monitored every 12 h for the first 3 days, and subsequently every 24 h. Probably, in same specific cases, a precise evaluation of the renal function would be done by Schwartz formula (Ccr) or cystatin C, but a multidisciplinary approach to evaluate this aspect of treatment is needed before considering it as a standard evaluation.

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