# Consensus conference on the management of tumor lysis syndrome

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## ABSTRACT

Tumor lysis syndrome is a potentially life threatening complication of massive cellular lysis in cancers. Identification of high-risk patients and early recognition of the syndrome is crucial in the institution of appropriate treatments. Drugs that act on the metabolic pathway of uric acid to allantoin, like allopurinol or rasburicase, are effective for prophylaxis and treatment of tumor lysis syndrome. Sound recommendations should regulate diagnosis and drug application in the clinical setting. The current article reports the recommendations on the management of tumor lysis syndrome that were issued during a Consensus Conference project, and which were endorsed by the Italian Society of Hematology (SIE), the Italian Association of Pediatric Oncologists (AIEOP) and the Italian Society of Medical Oncology (AIOM). Current concepts on the pathophysiology, clinical features, and therapy of tumor lysis syndrome were evaluated by a Panel of 8 experts. A consensus was then developed for statements regarding key questions on tumor lysis syndrome management selected according to the criterion of relevance by group discussion. Hydration and rasburicase should be administered to adult cancer patients who are candidates for tumor-specific therapy and who carry a high risk of tumor lysis syndrome. Cancer patients with a low-risk of tumor lysis syndrome should instead receive hydration along with oral allopurinol. Hydration and rasburicase should also be administered to patients with clinical tumor lysis syndrome and to adults and high-risk children who develop laboratory tumor lysis syndrome. In conclusion, the Panel recommended rasburicase for tumor lysis syndrome prophylaxis in selected patients based on the drug efficacy profile. Methodologically rigorous studies are needed to clarify its cost-effectiveness profile.

Key words: tumor lysis syndrome, rasburicase, lymphoma.

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## Introduction

Tumor lysis syndrome (TLS) is a potentially life threatening complication of massive cellular lysis in rapidly proliferating, bulky, or highly chemo-radiosensitive cancers.[1-4] TLS usually occurs during cytotoxic therapy and causes hyperuricemia, electrolyte disturbances (hyperkalemia, hyperphosphatemia, hypocalcemia), renal failure and overt organ damage (cardiac arrhythmia, seizures). Identification of high-risk patients and early recognition of the syndrome is crucial in the institution of appropriate treatments. Drugs that prevent the formation of uric acid or act on the metabolic pathway of uric acid to allantoin are effective for prophylaxis and treatment of TLS. In particular, allopurinol blocks the activity of the liver enzyme xanthine-oxidase, preventing the conversion of hypoxanthine and xanthine to uric acid and thereby decreasing the risk of uric acid crystallization in the kidneys.[5,6] Rasburicase, a recombinant urate-oxidase enzyme, converts existing uric acid to allantoin, which is 5 to 10 times more soluble in urine than uric acid.[7,8]

Rasburicase is considerably more expensive than allopurinol, therefore sound recommendations should regulate the diagnostic approach and the correct application of the available drugs in the clinical setting.

In order to improve awareness, diagnosis, and management of TLS, a Consensus Development Conference Project on TLS

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was convened. The conclusions of the project were endorsed by the Italian Society of Hematology (SIE), the Italian Association of Pediatric Oncologists (AIEOP) and the Italian Society of Medical Oncology (AIOM).

## Design and Methods

### Organization

Two chairmen (ST and GB) appointed an Expert Panel (EP) of 8 experts (5 hematologists, 1 pediatrician, 1 oncologist, 1 nephrologist), selected for their expertise in research and clinical practice of pediatric and adult malignancies. An Advisory Committee (AC) chaired by two clinicians with expertise in clinical epidemiology (GB and MM) supported the systematic review of literature and guaranteed the methodology of the process.

### Framing the domain of recommendations

During an initial meeting, the EP agreed on the goal of the project: to develop recommendations for the diagnosis, prophylaxis and therapy of TLS. The areas of major concern in the management of TLS were selected (defined as prevention of clinical and laboratory signs of TLS) by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, i.e. impact on patient outcome and risk of inappropriateness, through a Delphi process.[9] The 5 candidate key-questions that ranked highest formed the set of questions of the present recommendations.

### The Consensus process

During the first of three meetings, the EP examined the current state of knowledge regarding TLS. Each panelist drafted statements that addressed one of the 5 preliminarily identified key-questions. Subsequently, each panelist scored his/her agreement with the statements made by other panelists and provided suggestions for rephrasing. To facilitate this phase of the process, the EP was convened and three consensus conferences were held in Bologna, Italy, on 20th December 2006, 13th March 2007 and 22nd May 2007. The overall goals of the meetings were to reach a definite consensus over question-specific statements over which there had been disagreement during the first-round postal phase. The nominal group technique[10] was used by which participants were first asked to comment in "round robin" fashion on their preliminary votes and then to propose a new vote. If an 80% consensus on the statement was not achieved, the choices were discussed and a second vote taken. If an 80% consensus was still not attained, it was declared that no decision could be made on that issue.

## Results

### How should tumor lysis syndrome be defined and graded?

Only two reports have so far attempted to define and classify TLS. The first was a retrospective study performed in 105 NHL patients,[11] and the majority of the suggestions expressed in this paper were incorporated in more recent review articles[4,12] that contain the most widely accepted classification of TLS. The EP commented on the existence of some shortcomings in the definition of TLS. In particular, the Panel judged serum creatinine an inadequate means of evaluating renal dysfunction in this clinical setting. Since serum creatinine levels may also depend on patient age, hydration status, and muscular mass, the EP convened that glomerular filtration rate needed to be assessed in order to verify a clinical TLS. The EP also commented on the redundancy of TLS grade 0, which, according to Cairo and Bishop's definition, corresponds to no TLS.[4,12] Therefore, grade 0 TLS was not considered.

### Recommendations

*Laboratory TLS is defined by the occurrence of two or more of the following serum values before or after anticancer treatment (from three days before to seven days after the start of anticancer treatment):*

*(i) uric acid: increase by more than 25% from baseline (if a recent baseline value is available), or values ≥476 mmol/L (8 mg/dL); (ii) potassium: increase by more than 25% from baseline (if a recent baseline value is available), or values ≥6.0 mmol/L (6 mEq/L); (iii) phosphorus: increase by more than 25% from baseline (if a recent baseline value is available), or values ≥1.45 mmol/L (4.5 mg/dL) in adults and ≥2.1 mmol/L (6.5 mg/dL) in children; (iv) calcium: decrease by more than 25% from baseline (if a recent baseline value is available), or values ≤1.75 mmol/L (7 mg/dL).*

*Clinical TLS is defined by the presence of laboratory TLS and at least one of the following clinical alterations: renal failure (estimated glomerular filtration rate ≤ 60 mL/min), cardiac arrhythmia, seizure.*

*The Panel recommends a reliable measurement of renal excretory function.[13] The serum creatinine is widely used in diagnosing the presence of kidney injury. However, since it is a poor biomarker for acute kidney damage, different urinary and serum proteins such as urinary kidney injury molecule-1, plasma neutrophil gelatinase-associated lipocalin (NGAL), cystatin C and others, have been intensively investigated. Although there are promising candidate biomarkers, none are currently utilized clinically. Moreover, accurate measurement of kidney function is methodologically difficult in clinical practice so the creatinine clearance which requires a serum creatinine measurement and 24 hour urine collection is an acceptable surrogate. Alternate estimates of the glomerular filtration rate (eGFR) can be made by the Modification of Diet in Renal Disease Study Group (MDRD) formula or by the Cockroft and Gault equation.*

### eGFR using the MDRD formula

*eGFR (mL/min/1.73 $m^2$)=175 × serum creatinine (mmol/L) × 0.0113)$^{-1.154}$ 154 x age (years)$^{-0.203}$ × (0.742 if female).*

*Race multiplier 1 for all except black for whom it is 1.212.*

### Cockroft and Gault equation

Estimated creatinine clearance:

$$\frac{(140\text{-age}) \times \text{weight} \times 1.2 \times (0.85 \text{ if female})}{\text{Serum creatinine}}$$

Where age is espressed in years. Serum creatinine in mmol/L and weight in kg.

The Panel recommends estimating the glomerular fil-

tration rate of pediatric patients according to the Schwartz formula:[14]

*Estimated Glomerular Filtration Rate (mL/min) = 0.55 × length (cm) /serum creatinine (mg/dL)*

Grading of clinical TLS ranges from I to IV and corresponds to the highest grade of the observed clinical complications, i.e. seizures, cardiac arrhythmia and renal failure (Table 1).

### How should pre-treatment risk be assessed?

TLS tends to occur more frequently in hematologic malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with acute lymphoproliferative disorders with high proliferative rate and high tumor sensitivity to chemotherapy, like Burkitt's lymphoma and B-cell acute lymphoblastic leukemia (B-ALL), although TLS has also been recorded in other B-cell non-Hodgkin's lymphomas and T-ALL.[11,15,16] Tumor burden, reflected by serum lactate dehydrogenase (LDH) level, white blood cell count (initial count over 50,000/mm$^3$), extensive bone marrow involvement and tumor size, is the main predictor for development of TLS in these patients.[11,12,17]

Comorbidities predisposing to higher risk of developing TLS are elevated pre-treatment serum uric acid level, pre-existing renal damage, tumor infiltration in the kidney, obstructive uropathy, and advanced age.[11,12,17] Cytotoxic therapies more frequently associated with TLS are those employing highly active, cycle specific drugs (cytosine arabinoside, etoposide, cisplatin).[18] Corticosteroids have often been implicated in the pathogenesis of TLS probably because they are used as primary therapy for highly proliferating lymphoid disorders.[19] Less frequently, TLS has been reported after administration of intrathecal methotrexate[20] monoclonal antibodies (rituximab, gemtuzumab ozogamicin, campath), radiotherapy, interferon, thalidomide, hydroxyurea, fludarabine, imatinib, bortezomib,[21-25] and it has rarely been described also as a spontaneous event.[26] The Penn predictive score of tumor lysis syndrome (PPS-TLS) is a recently revised prognostic scoring system based on a single institution experience of 194 AML patients receiving induction chemotherapy.[27] Multivariate analysis showed that serum creatinine levels, serum urate levels and male gender were significant predictors, and all three variables were used to formulate a scoring system. The EP deemed that this scoring system, being derived only from patients with AML, could not be generally applicable. The same pitfalls can be observed in a more recent retrospective study performed in a larger series of adult AML patients.[28]

TLS is not a frequent complication in the treatment of adult solid tumors.[29,30] High-risk tumors include cancers known to be highly sensitive to chemotherapy, like bulky small cell lung cancer and metastatic germ cell carcinoma (either gonadal or extragonadal).[31,32] For other tumor types, bulky disease, especially in combination with massive liver metastases, can be considered a risk factor. Anedoctal cases of TLS after hormonal therapy for breast carcinoma and prostate cancer have also been documented.[33,34] In general, the TLS-related fatality rate is surprisingly high in adults with solid tumors (nearly 35%) compared to hematologic malignancies; the reasons might lie in an earlier initiation of prophylactic measures in hematologic patients and a general closer monitoring during and soon after chemotherapy.[29,30]

At the present time, there are no data to clearly set-up a comprehensive risk score classification for TLS in adult patients with solid tumors. Co-morbidities which may place a solid tumor patient at higher risk of developing TLS are: dehydration, hyponatremia,[35] pre-existing renal damage, hyperuricemia, obstructive uropathy. LDH level needs to be included in the work-up of cancer patients undergoing chemotherapy, since it generally reflects bulky disease and is considered a high-risk factor. High and rapid response to anticancer therapy (either with pharmacological treatment as well as with radiation therapy) has also to be included in the possible risk factors. As far as treatment modalities are concerned, nephrotoxic agents, such as cisplatin, have to be taken into account when evaluating patients' risk score.[36]

Children with malignancies have a 70% chance of



**Table 1.** Grading of clinical tumor lysis sindrome.

| | *I* | *II* | *III* | *IV* |
|---|---|---|---|---|
| Renal failure | Serum creatinine = 1.5 UNL or creatinine clearance 30-45 mL/min | Serum creatinine= 1.5-3 UNL or creatinine clearance 10-30 mL/min | Serum creatinine=3-6 UNL or creatinine clearance 10-20 mL/min | Serum creatinine >6 UNL or creatinine clearance <10 mL/min |
| Cardiac arrhythmia | Intervention not indicated | Non-urgent intervention indicated | Symptomatic and incompletely controlled or controlled with device (e.g. defibrillator) | Life threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock) |
| Seizure | None | One brief generalized seizure; seizure(s) well controlled by anti-convulsivant or infrequent focal motor seizures not interfering with ADL | Seizure in which consciousness is altered; poorly controlled seizure disorder, with breakthough generalized seizures despite medical intervention | Seizure of any kind which is prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy) |

EFS at ten years with the use of current multimodal and sometimes highly intensive chemotherapy protocols. Therapy-related morbidity and mortality have, for this reason, a substantial impact on the outcome of childhood cancer. TLS arises more frequently in children with tumors that have a high proliferative fraction, large tumor burden or wide dissemination and high chemosensitivity. For these reasons, this metabolic emergency occurs most commonly in Burkitt's lymphoma, lymphoblastic lymphoma, B-cell acute lymphoblastic leukemia (ALL) and T-cell ALL with hyperleukocytosis and extensive extramedullary disease.[37-39] In a recent paper, Wossmann *et al.*[40] analyzed the incidence and complications of TLS in 1,791 children with NHL enrolled in two subsequent multicenter studies. Out of this group, 78 (4.4%) developed a TLS and 42 (2.3%) oligo-anuria. 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 of developing a TLS (26.4%) and anuria (14.1%). Of the 790 patients with Burkitt's lymphoma or B-ALL, tumor burden, as indicated by LDH levels was the main predictor for the development of both TLS and anuria. The incidence of TLS was 1.2%, 12.7%, 19.1% for patients with LDH levels <500 U/L, 500-1,000 U/L and >1,000 U/L respectively. The incidence of TLS in patients with T-cell lymphoblastic lymphoma and other B-cell NHL was below 2% and anuria occurred in less than 1%. TLS is rare in acute myeloid leukemia (AML) despite the high blood cell count. TLS has also been documented in childhood solid tumor such as neuroblastoma, medulloblastoma and germ cell tumors.[41]

In the pediatric literature there are a few case reports of children who present hyperuricemia and acute renal failure as initial presentation of occult lymphoproliferative disorder.[42] Renal impairment at diagnosis appears to be the only relevant co-morbidity in stratifying pediatric patients at risk of TLS. Apart from renal failure, kidney(s) involvement at onset represents a rare but relevant risk factor.[37,43]

### Recommendations

*Patients at high risk of developing TLS carry at least one of the following factors: (i) Host-related factors (comorbidities): dehydration; hyponatremia (limited to solid tumors); pre-existing renal impairment (including renal infiltration by hematologic malignancies which induce a reduction in renal function); obstructive uropathy; hyperuricemia (uric acid >8 mg/dL in children and >10 mg/dL in adults). (ii) Disease-related factors (cancers with a high and rapid response to anticancer therapy): bulky disease (especially patients with bulky SCLC or concomitant massive liver metastases); metastatic germ cell tumor (either gonadal or extragonadal); high-grade lymphomas (in particular Burkitt's lymphoma and T-cell lymphoblastic NHL); acute lymphoblastic leukemia in adults and advanced T-cell ALL in pediatric patients; elevated serum LDH (>2 upper normal limit). (iii) Therapy-related factors: intensive polychemotherapy including cisplatin, cytosine arabinoside, etoposide, methotrexate.*

*The following evaluations should be made before starting antineoplastic therapy: creatinine clearance (or estimated GFR) and serum LDH levels in all patients, renal ultrasound in all high-risk pediatric patients. The Panel reached no consensus as to whether renal ultrasound was mandatory to assess pre-treatment TLS risk in adult patients.*

### When and which tumor lysis syndrome prophylaxis?

Prophylaxis is the best strategy to reduce the frequency and the severity of TLS episodes. The Panel agreed that prophylaxis of isolated hyperuricemia in cancer patients cannot be assimilated to TLS prophylaxis.

The first approach to TLS prophylaxis is vigorous hydration, i.e. no less than 2 L/m$^2$/day. Increased hydration and accompanying increase in urine flow improves intravascular volume, enhances renal blood flow and glomerular filtration, and promotes urinary excretion of uric acid and phosphate.[44,45]

Drugs for TLS prophylaxis include allopurinol, which blocks the activity of the liver enzyme xanthine oxidase, and thereby decreases the risk of uric acid crystallization in the kidneys,[5,6] and rasburicase, a recombinant urate oxidase enzyme, which converts existing uric acid to allantoin which is 5 to 10 times more soluble in urine than uric acid.[7,8] In patients with renal impairment, the allopurinol dosage must be adjusted due to accumulation of the drug and its metabolites. However, as in gouty patients with chronic kidney disease it is highly probable that also in TLS patients with kidney insufficiency higher therapeutic plasma oxipurinol concentrations might be required to meet the treatment goal.[46]

Few studies evaluated the efficacy of prophylactic use of rasburicase in patients at high risk of TLS. In a phase II dose finding study, all patients, including those treated at lower doses (0.15 mg/kg), achieved a significant and rapid decrease in uric acid level within four hours after rasburicase administration and none of the patients developed severe TLS or required dialysis.[47] A retrospective analysis carried out by Patte *et al*.[48] compared the rates of dialysis in the treatment of children treated for B-cell non-Hodgkin's lymphoma in the UK and in France. Patients in the French group received urate oxidase to prevent tumor lysis and those in the UK received allopurinol. Only 2.6% in the French group required dialysis compared with 16% in the UK. Urine alkalinization has historically been a general recommendation for the prevention and/or treatment of TLS. The use of sodium bicarbonate to alkalinize urine appears to be a reasonable approach as this will convert uric acid to the more soluble urate salt, thereby diminishing the tendency to uric acid precipitation in the renal tubules.[49] However, the current use of sodium bicarbonate to alkalynize the urine is controversial. The maximal solubility of urate occurs at a pH of 7.5 and at alkaline urine pH (6.5) the solubility of xanthine and hypoxanthine significantly decreases, leading to the development of urinary xanthine crystals during and after allopurinol therapy. Moreover, alkaline urine favors calcium phosphate precipitation in patients with increased serum calcium-phosphate cross-product.[50]

### Recommendations

*TLS prophylaxis is recommended to all pediatric patients and adult patients with hematologic malignancies undergoing chemotherapy. Patients who experienced TLS during previous*

*therapy lines can potentially go through another episode and in case salvage treatment needs to be started[51] these patients are thus candidates for prophylaxis. Patients with successful debulking of tumor mass and without end organ dysfunction secondary to previous TLS do not seem to benefit from any prophylactic measures once the offending condition(s) has been resolved.*

*It is suggested that nephrological consultation be taken before starting therapy in cases with previous episodes of clinical TLS before restarting therapy.*

*Low-risk pediatric and adult patients should receive oral allopurinol, hydration and urine alkalinization.*

*High-risk patients should receive rasburicase and hydration in an inpatient setting. At the end of the treatment with rasburicase, patients should start receiving oral allopurinol. Rasburicase should be administered at the dose of 0.20 mg/kg/day, infused over 30 minutes, administering the first dose at least four hours before the start of tumor-specific therapy and continuing for at least 3-5 days. Application of lower doses of rasburicase for TLS prophylaxis are still under evaluation. In order to avoid xanthine accumulation and lack of substrate for rasburicase, concomitant allopurinol should not be administered.*

*Allopurinol should be administered orally at the dose of 100 mg/m$^2$ thrice daily (maximum 800 mg/day).*

*Rasburicase is contraindicated in patients with metahemoglobinemia, G6PDH deficiency or other metabolic disorders that can potentially cause hemolytic anemia; these patents should be treated with oral allopurinol, hydration and urine alkalinization.*

*When possible, hydration should start at least 48 hours before tumor-specific therapy; however, the use of rasburicase with subsequent rapid degradation of uric acid allows earlier administration of chemotherapy, if needed. Urine output should be kept at least 100 mL/hour in adults (3 mL/kg/hour in children <10 kg body weight). The state of hydration is extremely important in optimizing urine output. The measurement of urine osmolality and fractional excretion of sodium may be helpful in defining the hydration status. Loop diuretics may be required in order to maintain this urine output, except for patients with concomitant obstructive uropathy or hypovolemia. The hemodynamic status and the hydration level of the patient should be checked before loop diuretics should be used.*

*Unless other clinical conditions require urine alkalinization, urines should not be alkalinized in patients who receive concomitant rasburicase therapy.*

### Which monitoring approach for tumor lysis syndrome?

No studies have been published investigating the best monitoring approach and the appropriate related time periods in patients at risk of TLS. The Panel provided recommendations based on good clinical practice principles.

### Recommendations

*In patients at high risk of TLS, levels of LDH, uric acid, sodium, potassium, creatinine, BUN, phosphorus and calcium should be monitored every 12 hours for the first three days, and every 24 hours subsequently.*

*In patients with TLS, the following parameters should be monitored every six hours for the first 24 hours and daily subsequently: vital parameters (heart rate, blood pressure, urine output, respiratory rate), serum uric acid level, serum electrolytes (phosphate, calcium, potassium), renal function (serum creatinine, BUN, urine pH and osmolality, urine specific gravity). Blood cell count, serum LDH, albumin, serum osmolality, blood gases and acid-base equilibrium, electrocardiogram, and body weight should be assessed every 24 hours.*

### Which tumor lysis syndrome therapy?

Clinical TLS is an emergency that can lead to death or can severely impair the possibility of the patients receiving an adequate cytotoxic therapy. It is thus mandatory to achieve a rapid relief of all the symptoms and a prompt correction of all the metabolic alterations related to TLS. Urine alkalinization has traditionally represented a cornerstone of TLS treatment as it increases uric acid solubility. However, it has some major drawbacks, including increased precipitation of calcium phosphate and reduced xanthine solubility. Furthermore, alkalinization does not provide any advantage in improving biochemical abnormalities of TLS, therefore, its use has been progressively abandoned, particularly since the availability of rasburicase.[52] Another controversial issue is the use of calcium gluconate: this measure is not recommended to correct mild hypocalcemia as it leads to increased tissue and renal precipitation of calcium phosphate. But it is a potentially useful supportive therapy for hyperkalemia-induced cardiac arrhythmias.[53]

As regards the treatment of hyperuricemia, allopurinol can reduce the formation of uric acid but is not able to degrade it, and this implies a significant delay in the resumption of chemotherapy. Rasburicase affects a rapid and complete degradation of uric acid to allantoin thus potentially allowing a prompt continuation of chemotherapy.[7,8] No randomized study aimed at comparing rasburicase with allopurinol has so far been performed in adult patients with TLS. Several single-arm either compassionate or phase I-II trials have shown that this drug is active in reducing uric acid levels with a favorable safety profile.[54-57] Alternative schedules of administration have been recently proposed; however, only a small fraction of the reported patients presented with metabolic abnormalities other than hyperuricemia, so more data are needed to support the possible use of these schedules even in overt TLS.[58,59]

Studies comparing rasburicase with allopurinol in the treatment of pediatric patients with hyperuricemia due to TLS have shown better results with rasburicase. In a study by Bosly *et al.*,[56] 166 pediatric patients who had leukemia (74%), lymphoma (24%), or solid tumors (3%) were treated with rasburicase. Mean serum uric acid level in 29 hyperuricemic children decreased from 15.1 to 0.4 mg/dL. In another study by Pession and Barbieri,[60] 26 children with malignancy at risk of TLS were submitted to treatment (group 1) or prophylaxis (group 2) of acute hyperuricemia with rasburicase. The drug significantly decreased serum uric acid in all patients. Control of serum uric acid was obtained in both groups within 24 hours of the first dose with a response rate of 100% (group 1) and 93% (group 2). In a study by Shin *et al.*,[61] serum uric acid endpoint (≥7.0 mg/dL) was reached in 97.3% of the patients and serum uric acid levels were significantly reduced in all patients ($p$<0.001). In a randomized prospective trial, children with hematologic malignancies at high risk of TLS

(newly diagnosed ALL or stage III/IV NHL) were stratified and randomized to receive rasburicase or allopurinol.[62] Results showed that the 27 patients who received rasburicase had a significantly lower serum uric acid and a significantly lower mean uric acid area under the curve measured from 0 to 96 hours (128±70 mg/dL/hour *vs.* 329±129 mg/dL/hour; $p<0.001$).

As laboratory TLS implies the presence of at least 2 biochemical alterations among hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia, treatment of laboratory TLS is superimposable to treatment of clinical TLS.

### Recommendations

*Hydration through a central venous access and rasburicase should be administrated to all patients with clinical TLS.*

*Hydration and rasburicase should also be administrated to adults with laboratory TLS, children with high risk of TLS or children with a rapid worsening of biochemical parameters of TLS.*

*When possible, hydration should start at least 48 hours before tumor-specific therapy; however, the use of rasburicase with subsequent rapid degradation of uric acid allows earlier administration of chemotherapy, if needed. Urine output should be kept at least at 100 ml/hour (3 mL/kg/hour in children <10 kg body weight). Loop diuretics (or mannitol) may be required in order to maintain this urine output, except for patients with concomitant obstructive uropathy or hypovolemia.*

*The schedule and contraindications for rasburicase administration should be the same as those for prophylaxis. Mild hyperphosphatemia (< 1.62 mmol/L) does not require treatment or can be treated with aluminum hydroxide at 50-100 mg/kg/day divided in 4 doses that can be administered orally or by nasogastric tube.*

*Asymptomatic hypocalcemia does not require treatment. In case of symptoms, such as tetany and seizures, a single dose of calcium gluconate 50-100 mg/kg should be infused and cautiously repeated if necessary.*

*Mild (< 6mmol/L) asymptomatic hyperkalemia can be corrected with hydration, loop diuretics and sodium polystirene 1 g/kg either orally or by enema. For more severe hyperkalemia, rapid insulin (0.1 units/kg) plus glucose (25% dextrose 2 mL/kg) is also suggested; further interventions include calcium carbonate 100-200 mg/kg/dose and sodium bicarbonate to stabilize myocardial cell membrane and to correct acidosis. Careful ECG monitoring should be peformed in hyperkalemic patients.*

## When are dialytic procedures for tumor lysis syndrome appropriate?

The release of intracellular nucleic acids following effective cytotoxic therapy results from the lysis of large numbers of tumor cells and can produce high uric acid concentrations that facilitate crystallization in the collecting ducts and the deep cortical and medullary vessels, causing acute oliguric renal failure and anuria. Kidney injury may be aggravated by the appearance of hyperphosphatemia.[63] High serum phosphate concentrations and calcium phosphate complexes deposited in the renal interstitium and the tubular system are the possible mechanisms exacerbating kidney damage. The early start of renal replacement therapy has been advised to remove purine by-products and to improve hyperphosphatemia, hyperkalemia, and hypocalcemia associated with TLS.[64] Oliguria due to acute uric acid nephropathy rapidly responds to hemodialysis (HD) often restarting diuresis as the plasma uric acid level falls to 10 mg/dL. Molecules, such as uric acid and phosphate, are effectively removed by diffusive therapy and intermittent hemodialysis (IHD). In HD, uric acid clearance is approximately 70-100 mL/min and the plasma uric acid level falls by about 50% with each 6-hour treatment. However, renal replacement techniques have to be applied in TLS characterized not only by sudden increase in uric acid but also by the presence of acid-base and electrolyte abnormalities and the appearance of oliguria and extracellular fluid volume overload. As well as the suggestion that daily HD may provide an improved outcome in end-stage renal disease, it is conceivable that more frequent dialysis treatments may well improve the course of TLS with kidney damage. Apart from conventional HD, multiple therapy modalities may be used in the management of TLS, including peritoneal dialysis (PD), continuous renal replacement therapies (CRRT), and new *hybrid* therapies, such as sustained, low-efficiency dialysis and extended daily dialysis. CRRT, as compared with IHD, are associated with a greater improvement in hemodynamic instability, azotemia and fluid overload control, as well as a better nutritional support. However, there are no studies evaluating and comparing outcomes with IHD and CRRT in TLS.

Peritoneal dialysis (PD) is seldom used in the management of TLS. The major drawback to the use of PD in TLS is the lower efficiency of PD in removing solute and fluid as compared with IHD and CRRT. This limits its usefulness in patients who require a significant solute removal (uric acid, urea) and electrolytes (potassium, phosphate).

There are no data to compare conservative treatment with pre-emptive dialysis and to develop reliable clinical profiles for identifying patients at risk of developing renal failure and subsequent complications. However, decreased renal function with advanced age and associated co-morbidities (diabetes, cardio-vasculopathy) may be responsible for a higher incidence of acute renal failure.

### Recommendations

*Indications for the start-up of renal replacement therapy in TLS include persistent hyperkalemia, severe metabolic acidosis, volume overload unresponsive to diuretic therapy, and overt uremic symptoms, including pericarditis and severe encephalopathy.*

*Dialysis may be initiated "prophylactically" before the development of overt uremic symptoms in response to severe, progressive hyperphosphatemia (>6 mg/dL) or severe symptomatic hypocalcemia.*

*The appropriate timing for this criterion remains unresolved.*

*Frequent (daily) dialyses are recommended considering the continuous release into the bloodstream of purine-products, potassium, and other metabolites and electrolytes resulting from lysed tumor cells. The timing of dialysis and the dialysis dose should be linked to the purine generation rate.*

*Potential indications for CRRT in patients with TLS include the appearance of pulmonary edema, maintaining fluid balance, facilitating the delivery of nutritional therapy, improving*

*gas-exchange in ARDS patients and removing inflammatory mediators in sepsis and MOF patients.*

*Potential candidates for CRRT are hemodynamically unstable patients, as CRRT can be more safely performed due to a diminished tendency to exacerbate hypotension.*

*In centers unequipped to perform CRRT, long-duration daily dialysis may be a good alternative in patients with cardiovascular instability.*

*Peritoneal dialysis should be reserved for situations where other therapy modalities are unavailable.*

### Pharmaco-economic issues

Intravenous rasburicase is approved in the US and the EU for the management of acute hyperuricemia in pediatric patients and adult patients (in the EU only) with hematologic malignancies or solid tumors who are at risk of anticancer therapy induced TLS and elevated plasma uric acid concentrations. The pharmaco-economics of rasburicase and its administration has been considered in relation to that of allopurinol. A secondary economic evaluation assessed the cost-effectiveness of intravenous rasburicase based on a retrospective review of data from charts of pediatric and adult patients with acute lymphocytic leukemia, acute myeloid leukemia or non-Hodgkin's lymphoma in the UK, the Netherlands, Spain and Belgium.[65,66] Health care resource-related costs attributable to treatment include medications, interventions, consultations, laboratory monitoring, imaging, and hospitalization.[65-67] The cost of hyperuricemia and TLS were calculated from the health care payer perspective-based resource use, and the cost of rasburicase treatment was based on the average treatment duration (3-4 days) and body weight of patients in the compassionate-use programs. The incremental cost-effectiveness ratios (ICERs) for prevention and treatment of hyperuricemia and TLS with rasburicase were calculated per life-year saved (LYS) considering costs, probability of development of hyperuricemia and TLS, and the percentage of these conditions prevented by rasburicase. Rates of 100% and 90% were assumed for preventions of TLS and hyperuricemia with rasburicase. A threshold of 31,600 euros (€) per LYS was considered acceptable. Rasburicase was highly cost-effective for prevention of TLS and hyperuricemia in children (ICER between €425 and €3054 per LYS) regardless of the malignancy. Treatment of TLS and hyperuricemia with rasburicase in children was cost-saving (i.e. less costly and more effective than allopurinol). In adults, the cost-effectiveness of rasburicase for prevention of TLS and hyperuricemia depended on the malignancy (ICER between €23,794 and €101,734 per LYS), whereas the cost-effectiveness of treatment of these conditions appeared to be independent of the malignancy. The ICERs of rasburicase for prevention or treatment of TLS were influenced by variables such as the life expectancy of patients incidence and percentage of TLS cases that were avoided with rasburicase treatment. Rasburicase was less cost-effective when there was a lower incidence of TLS.

Many pharmaco-economic issues remain to be solved. Studies that determine the cost-effectiveness of the treatment in patients at intermediate risk of TLS, e.g. acute myeloid leukemia or non-B-cell ALL, are lacking and this could be tackled by a randomized study.

## Discussion

Although TLS is a rare event, occurring in 5-20% of cancer patients,[11,12,43-45] it represents a serious complication that can potentially lead to death. It is, therefore, mandatory for the treating physician to recognize risk factors, and to set up prophylaxis and treatment of TLS in order to offer patients the opportunity to receive an adequate therapy for their neoplasm. This issue is particularly important for pediatric patients who in up to 70% of the cases can be cured with appropriate chemotherapy regimens.

The existing scientific literature on the management of TLS does not provide strong evidence-based recommendations on diagnosis, risk stratification, prophylaxis, monitoring and therapy. In this work, experts of the field judged whether the body of evidence was sufficient to provide any recommendation in a decision process grounded on the concept that the relative benefit-to-risk balance of any decision results from a partially subjective process. As a consequence, consensus was a critical part of the present recommendation production. This document was mainly based upon the experience and knowledge of experts in the field co-ordinated by the methods of group decision.

As regards prophylaxis, the present recommendations were aimed at increasing physician awareness of risk factors associated with TLS and of the most appropriate measures to avoid the occurrence of overt TLS. The most obvious limitation of these recommendations was the small number of literature reports on solid tumors and on the occurrence of TLS on *targeted therapy*, i.e. using novel drugs that are highly tumor-specific. This latter issue should, therefore, be considered a topic for further research.

In the context of recommendations for TLS therapy, the use of dialytic procedures was analyzed and discussed, and this issue is relatively new when compared to the existing literature in the field. It was not intended as a substitute for nephrology consultation but it has the purpose of making the treating physician aware of these measures in order to improve patients' outcome.

Finally, the most appropriate use of the available drugs aimed at reducing hyperuricemia, allopurinol and rasburicase, was discussed both in prophylaxis and in a therapeutic setting, and an analysis of pharmaco-economic issues was also performed. Rasburicase is the drug of choice for TLS therapy and for TLS prophylaxis in high-risk patients, while allopurinol should be administered for prophylaxis in low-risk patients and in case of metabolic contraindication to rasburicase.

Evaluation of different dosing and schedules of rasburicase administration should be considered another topic for further research.

## Authorship and Disclosures

Two chairmen (ST and GB) appointed the Expert Panel (EP) that included 5 hematologists (PT, VL, EM, PLZ and the same ST), 1 pediatrician (AP), 1 oncologist

(GR), 1 nephrologist (AS), 1 expert in clinical epidemiology (MM) and 1 health economist (CL). All the authors participated in the Panel meetings, and gave a significant contribution in drafting the paper and giving the final approval. This consensus conference was supported by an unrestricted educational grant from Sanofi-Aventis, which sells rasburicase.

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