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Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus

Mitchell S. Cairo,[1]* Bertrand Coiffier,[2] Alfred Reiter[3] and Anas Younes[4] on behalf of the TLS Expert Panel

[1]Departments of Pediatrics, Medicine and Pathology, Columbia University, Morgan Stanley Children's Hospital, NY-Presbyterian, NY, USA, [2]Department of Haematology, Hospices Civils de Lyon and University Claude Bernard, Lyon, France, [3]Children's University Hospital, Division of Paediatric Haematology and Oncology, Justus-Liebig University, Giessen, Germany, and [4]The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

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Correspondence: Mitchell S. Cairo, MD, Chief, Division Blood and Marrow Transplantation, Professor, Pediatrics, Medicine & Pathology, Morgan Stanley Children's Hospital, New York Presbyterian, Columbia University, New York, NY, USA. E-mail: mc1310@columbia.edu

*All authors contributed equally to this manuscript.

Summary

Tumour lysis syndrome (TLS) is a life-threatening oncological emergency characterized by metabolic abnormalities including hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. These metabolic complications predispose the cancer patient to clinical toxicities including renal insufficiency, cardiac arrhythmias, seizures, neurological complications and potentially sudden death. With the increased availability of newer therapeutic targeted agents, such as rasburicase (recombinant urate oxidase), there are no published guidelines on the risk classification of TLS for individual patients at risk of developing this syndrome. We convened an international TLS expert consensus panel to develop guidelines for a medical decision tree to assign low, intermediate and high risk to patients with cancer at risk for TLS. Risk factors included biological evidence of laboratory TLS (LTLS), proliferation, bulk and stage of malignant tumour and renal impairment and/or involvement at the time of TLS diagnosis. An international TLS consensus expert panel of paediatric and adult oncologists, experts in TLS pathophysiology and experts in TLS prophylaxis and management, developed a final model of low, intermediate and high risk TLS classification and associated TLS prophylaxis recommendations.

Keywords: tumour lysis syndrome, risk, malignancy, prophylaxis.

It is essential to identify patients at risk of tumour lysis syndrome (TLS) because this life-threatening condition may occur rapidly and is preventable. However, standardized procedures for assessing risk have been lacking until now. The new, comprehensive TLS risk classification system reported here for adults and children accounts for all malignancies and known risk factors, integrating them into a simple and easy to use clinical tool that provides a basis for recent TLS management guidelines as well as future TLS studies.

TLS is a group of metabolic abnormalities that result from the rapid release of intracellular metabolites such as nucleic acids, proteins, phosphorus and potassium from lysed malignant cells. This process can potentially cause hyperuricaemia, hyperkalaemia, hyperphosphataemia, with or without hypocalcaemia and uraemia that can lead to renal failure, arrhythmias, seizures and even death. TLS symptoms can occur spontaneously or within 12–72 h after initiation of cytoreductive chemotherapy and require prompt recognition followed by aggressive management. Complications resulting from TLS, can compromise the efficacy or further administration of chemotherapy (Levine, 2002; Yim *et al*, 2003; Hsu *et al*, 2004) and have an impact on morbidity and mortality. They are also associated with longer and more costly hospital stays (Annemans *et al*, 2003; Candrilli *et al*, 2008).

TLS is most frequently associated with non-Hodgkin lymphoma (NHL), particularly Burkitt lymphoma/leukaemia, as well as other haematological malignancies, such as acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), after initiation of cytotoxic treatment (Annemans *et al*, 2003; Akoz *et al*, 2007; Coiffier *et al*, 2008; Hochberg & Cairo, 2008; Konuma *et al*, 2008; Chen & Chuang, 2009; Choi *et al*,

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2009). In an observational study of patients with AML (Montesinos *et al*, 2008), TLS was observed in 130 (17%) out of 772 patients and was considered the major cause of death in 2% of patients. An overall TLS incidence of 4·4% was reported in two multicentre studies of 1791 children and adolescents with NHL (Wossmann *et al*, 2003) and, of these, TLS occurred in 8·4% (66 out of 790) of patients with Burkitt lymphoma/leukaemia or B-cell ALL (B-ALL). TLS may also occur in other tumour types, especially tumours sensitive to cytotoxic treatment, that have a high proliferative rate or have a large tumuor size or burden (Coiffier *et al*, 2008). Unexpected cases of TLS where a high TLS risk was not immediately evident and for which appropriate risk assessment and management could make the difference between life and death have also been reported (Kalemkerian *et al*, 1997; Vaisban *et al*, 2001; Francescone *et al*, 2009; Lin *et al*, 2009). For example, an adult patient with end-stage renal disease and diffuse large B-cell lymphoma (DLBCL) developed acute TLS after receiving low dose COP chemotherapy (cyclophosphamide, vincristine and dexamethasone) and allopurinol (Lin *et al*, 2009). A computed tomography scan revealed a retroperitoneal mass ($8{\cdot}5 \times 9{\cdot}5$ cm^2) while laboratory values on presentation included a creatinine level of 566 μmol/l and a lactate dehydrogenase (LDH) level of 523 u/l. In another case, an adult patient with chronic lymphocytic leukaemia (CLL) and pre-existing asotemia developed acute TLS and renal failure after initiation of high-dose corticosteroid therapy (Vaisban *et al*, 2001). Both of these cases highlight that overall TLS risk derives from the collective contribution of several individual risk factors and underline the critical need for a risk model that integrates them in order to identify high TLS risk, even in unusual settings. Risk factors for TLS include age, type of malignancy, tumour burden (stage/LDH), white blood cell (WBC) counts and whether renal function is compromised (Michallet *et al*, 2005; Coiffier *et al*, 2008). Some risk stratification systems have been developed by regional entities, but each system addresses different diseases, uses different criteria and establishes different thresholds for risk (Seidemann *et al*, 1998; Wossmann *et al*, 2003; Bertrand *et al*, 2008; Coiffier *et al*, 2008; Montesinos *et al*, 2008; Tosi *et al*, 2008). TLS risk guidelines (Bertrand *et al*, 2008) developed by the French Society for the Prevention of Cancer in Children and Adolescents (SCFE) only addressed T-cell lymphoma, B-cell lymphoma, ALL and AML and did not assess TLS risk in adult patients. Similarly, the TLS risk stratification system developed by the Berlin–Frankfurt–Münster (BFM) Group is restricted to children (Seidemann *et al*, 1998; Wossmann *et al*, 2003) and focuses only on B-NHL and T-LBL, while recent guidelines proposed by an international panel of experts (Coiffier *et al*, 2008) do not address all malignancies or uniformly assess risk based on renal involvement/function. Consequently, none of these guidelines can be uniformly applied to all patients at risk of developing TLS. The need for a straightforward and unifying risk stratification model is particularly important for TLS because it is encountered almost exclusively by physicians with a haematology/oncology, nephrology and/or emergency room background.

Methods

To address this unmet need an international panel of experts (Appendix I) met in Paris in November 2008 to reach a consensus concerning a comprehensive TLS risk classification system based on the peer-reviewed literature, standards of practice and clinical experience. The panel was chosen for their expertise in adult and paediatric malignancies as well as TLS pathophysiology and management. A review of the literature for the last 43 (1966–2009) years on the incidence, prophylaxis and treatment of TLS was conducted by the TLS expert panel. Both an evidenced-based literature and expert opinion-based approach was utilized (Tables I and II).

A preliminary version of the proposed TLS risk evaluation model was produced in advance of this meeting by a steering committee. Low-risk disease (LRD) was defined as an approximate risk of less than 1% of developing TLS, intermediate risk disease (IRD) was defined as a risk of approximately 1–5% of developing TLS and high risk disease (HRD) was defined as a risk of greater than 5% (>5%) of developing TLS based on the incidence defined in the literature (Annemans *et al*, 2003; Wossmann *et al*, 2003; Akoz *et al*, 2007; Coiffier *et al*, 2008; Konuma *et al*, 2008; Montesinos *et al*, 2008; Chen & Chuang, 2009; Choi *et al*, 2009). Each proposed recommendation was discussed at length by the entire expert panel during the meeting and required consensual agreement by all panel members before being included in the final model.

The diverse specialties of the panel ensured that the risk stratification model reflected best clinical practice and addressed the issues and concerns relevant to each specialty. Furthermore, this risk model complements and builds upon recent guidelines for the diagnosis and management of paediatric and adult TLS proposed by Coiffier *et al* (2008).

Results

TLS risk classification model

TLS risk evaluation was based on three sequential phases, which collectively defined the final evaluation of TLS risk. Firstly, patients were assessed for the presence of laboratory TLS (LTLS) (Hande & Garrow, 1993; Cairo & Bishop, 2004). Patients were required to have two or more abnormalities of uric acid (increased), potassium (increased), or phosphate (increased) in order to be defined as LTLS (Cairo & Bishop, 2004). Next, haematological malignancies and solid tumours were classified as LRD, IRD or HRD. Patients were also stratified by age and stage, bulk disease, WBC count and LDH level. The third step required an adjustment to be made based on renal function and renal involvement, and patients would then be finally classified as having a high risk, intermediate risk or low risk of developing TLS.

Table I. Levels of evidence.

1++	Meta-analyses, systematic reviews or randomized clinical trials with low risk of bias
1+	Meta-analyses, systematic reviews or randomized clinical trials with high risk of bias
2++	Systemic reviews or case-control or cohort studies with a high probability that relationship is causal
2+	Systemic reviews or case-control or cohort studies with a low probability that relationship is causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

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Table II. Grades of recommendation.

A	At least one meta-analysis, systematic review or randomized clinical trial rated as 1++ and directly applicable to population, or A systematic review of randomized clinical trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating consistency of results.
B	A body of evidence rated as 2++ directly applicable to target population and demonstrating overall consistency of results, or Extrapolated evidence from studies with level of evidence as 1++ or 1+
C	A body of evidence rated as 2+, directly applicable to target population and demonstrating consistency of results, or Extrapolated evidence from studies rated as 2++
D	Level of evidence 3 or 4, or Extrapolated evidence from studies rated as 2+

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Biological signs of TLS

In the present model LTLS was diagnosed by one of three clinical scenarios. Serum uric acid levels were within normal limits but serum phosphate and potassium levels exceeded the upper limit of normal. LTLS was also diagnosed when uric acid levels were above the upper limit of normal and concurrently either phosphate or potassium levels were above the upper limit of normal. An elevated uric acid, potassium and phosphate has previously been determined to be ≥476 μmol/l or ≥25% increase from baseline, ≥6·0 mmol/l or ≥25% increase from baseline and ≥2·1 mmol/l or ≥25% increase from baseline, respectively (Cairo & Bishop, 2004). During the time period where patients are at risk of developing LTLS, electrolyte and chemistry monitoring should be conducted at least every 6 h or earlier, depending on the clinical condition of the patient. Calcium levels were not included as a criterion for establishing LTLS in this risk classification system because hypocalcaemia may not be considered a direct consequence of TLS and is associated with high phosphate levels in the vast majority of cases (Navolanic *et al*, 2003). This TLS risk classification model should not be used for patients with pre-existing elevated uric acid levels due to gout prior to the diagnosis of their malignancy.

Risk assessment based on malignant disease type

Most solid tumours were classified as LRD (Fig 1). However, bulky solid tumours that were sensitive to chemotherapy, such as neuroblastoma, germ-cell tumours and small-cell lung cancers, were classified as IRD. In general, most solid tumours were at very low risk of developing TLS (LRD) (Drakos *et al*, 1994; Kalemkerian *et al*, 1997; Baeksgaard & Sorensen, 2003; Vaisban *et al*, 2003; Tosi *et al*, 2008). Myelomas were also classified as LRD (Fig 1).

The panel subdivided leukaemias into two categories: chronic and acute leukaemias. Chronic myeloid leukaemia (CML) was an LRD (Fig 1) in the present risk classification system. To take into account the therapy-dependent risk for TLS in patients with CLL (Cheson *et al*, 1998; Dillman & Hendrix, 2003; Hussain *et al*, 2003; Hummel *et al*, 2005; Calvo-Villas *et al*, 2008; Lin, 2008; Phelps *et al*, 2009), CLL was an LRD when treated exclusively with alkylating agents, but an IRD in the presence of an elevated WBC ($\geq 50 \times 10^9$/l) and/or were treated with targeted and/or biological therapies (fludarabine/rituximab).

Acute leukaemias were divided into three categories: AML, ALL and Burkitt lymphoma/leukaemia (B-ALL) (Fig 2). The risk of TLS was assessed in each of these categories, based on WBC counts and LDH levels, as both factors correlated with TLS risk (Navolanic *et al*, 2003; Truong *et al*, 2007; Montesinos *et al*, 2008). This is the first risk classification system that takes into account all of these variables for all types of leukaemia. AML was either an LRD, IRD or HRD, depending on WBC counts and LDH levels. Similarly ALL was an IRD or HRD depending on WBC counts and LDH levels (Fig 2). B-ALL was always considered an HRD.

The panel classified Hodgkin, small lymphocytic, follicular, marginal zone B-cell, mucosa-associated lymphoid tissue, mantle cell (non-blastoid variants) and cutaneous T-cell lymphomas as LRDs (Fig 3A). The panel decided to classify early-stage Burkitt lymphoma/leukaemia and lymphoblastic lymphomas as IRD, except when LDH levels were twice or more above the upper limit of normal, in which case they were HRD. Advanced-stage Burkitt lymphoma/leukaemia and lymphoblastic lymphomas were always considered as HRD.

Anaplastic large cell lymphoma (ALCL) was an LRD in children with stage I and II disease and an IRD in children with stage III or stage IV disease. ALCL was an LRD in adults, irrespective of disease staging (Fig 3B). Adult T-cell (ATL), DLBCL, peripheral T-cell, transformed and mantle cell (blastoid variants) lymphomas were classified as either LRD,

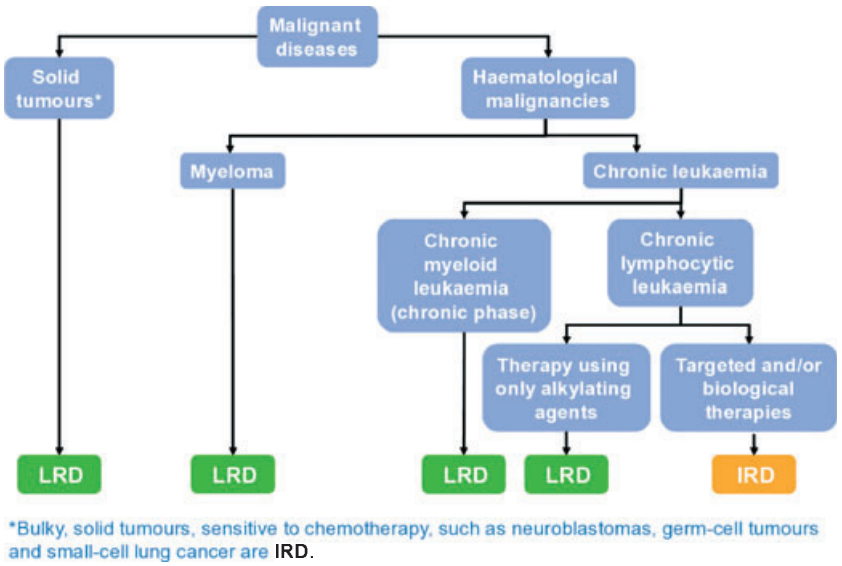

Fig 1. TLS risk assessment of solid tumours, myelomas and chronic leukaemias. Most solid tumours are low-risk diseases (LRD). Bulky, solid tumours that are sensitive to chemotherapy are intermediate-risk diseases (IRD). Myelomas are LRD. Risk classification of chronic leukaemia varies according to type of leukaemia and treatment strategy.

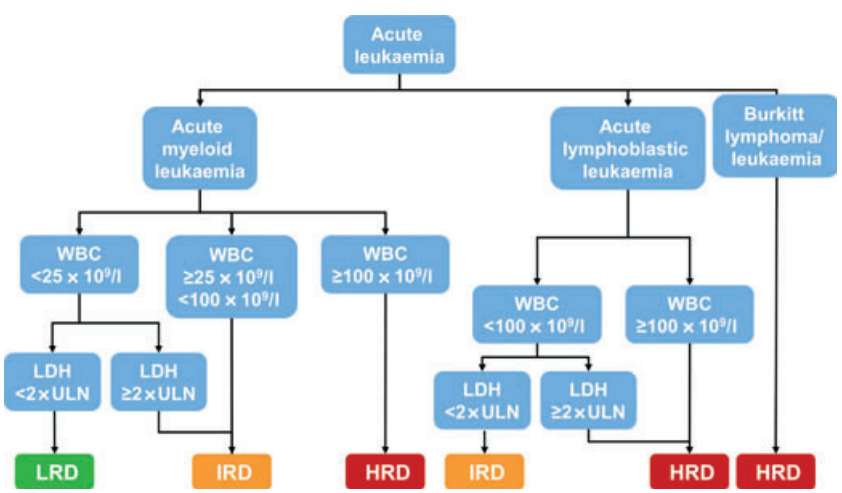

Fig 2. TLS risk assessment for acute leukaemia. Classification of acute myeloid leukaemia and acute lymphoblastic leukaemia depends on white blood cell (WBC) counts and lactate dehydrogenase (LDH) levels. Burkitt lymphoma/leukaemia is always classified as an HRD. LRD, low risk disease; IRD, intermediate risk disease; HRD, high risk disease.

IRD or HRD, depending on patient age, LDH levels, disease staging and tumour bulk (Fig 3B). Finally, myelomas were classified as LRD (Fig 1).

Adjustment of TLS risk based on renal function and/or involvement

Several renal conditions may predispose patients to developing TLS, such as pre-existing uraemia or hyperuricaemia, decreased urinary flow or acidic urine, dehydration, oliguria, anuria and renal insufficiency or renal failure (DeConti & Calabresi, 1966; Arseneau *et al*, 1975; Landgrebe *et al*, 1975; Tsokos *et al*, 1981; Kunkel *et al*, 2000; Annemans *et al*, 2003; Bosly *et al*, 2003; Cairo & Bishop, 2004). Apart from renal failure, kidney(s) involvement at diagnosis represents a rare but significant risk factor (Stapleton *et al*, 1988; Locatelli & Rossi, 2005).

In the proposed classification system, this final level aggregated all individual risk factors described above, plus renal risk factors, for the final classification of patients. This is the first TLS risk classification system that combines multiple factors into a final assessment of the patient's risk of developing TLS rather than restricting analysis to individual parameters. Consequently, patients with lymphomas or leukaemias considered to be LRDs, were classified as being at an intermediate risk of developing TLS if there was renal dysfunction and/or renal

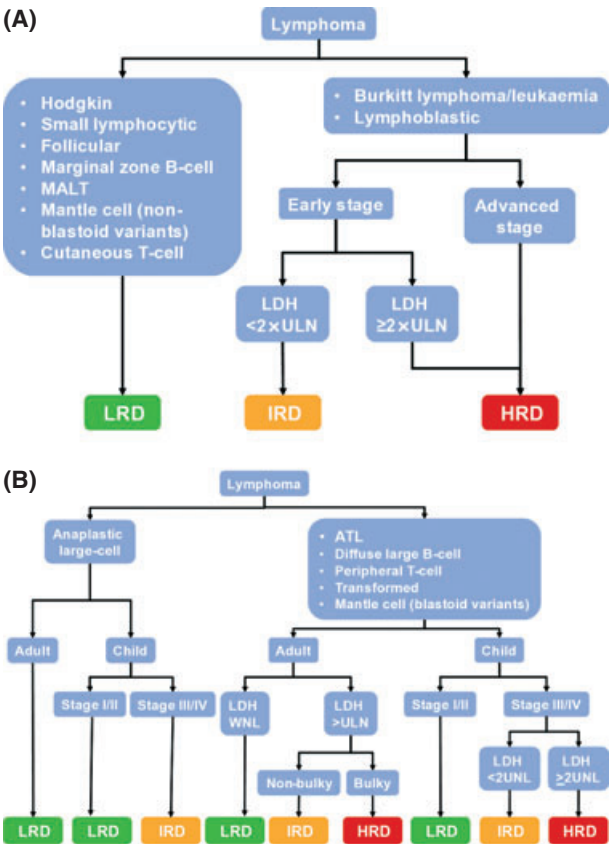

Fig 3. TLS risk assessment for lymphomas. (A) Some types of lymphomas are always classified as LRD, whereas classification of Burkitt lymphoma/leukaemia and lymphoblastic lymphomas depends on the stage of the disease and lactate dehydrogenase (LDH) levels. (B) Other types of lymphomas are classified according to patient age, stage of disease, tumour mass and LDH levels. ATL, adult T-cell lymphoma; WNL, within normal limits; ULN, upper limit of normal; LRD, low risk disease; IRD, intermediate risk disease; HRD, high risk disease.

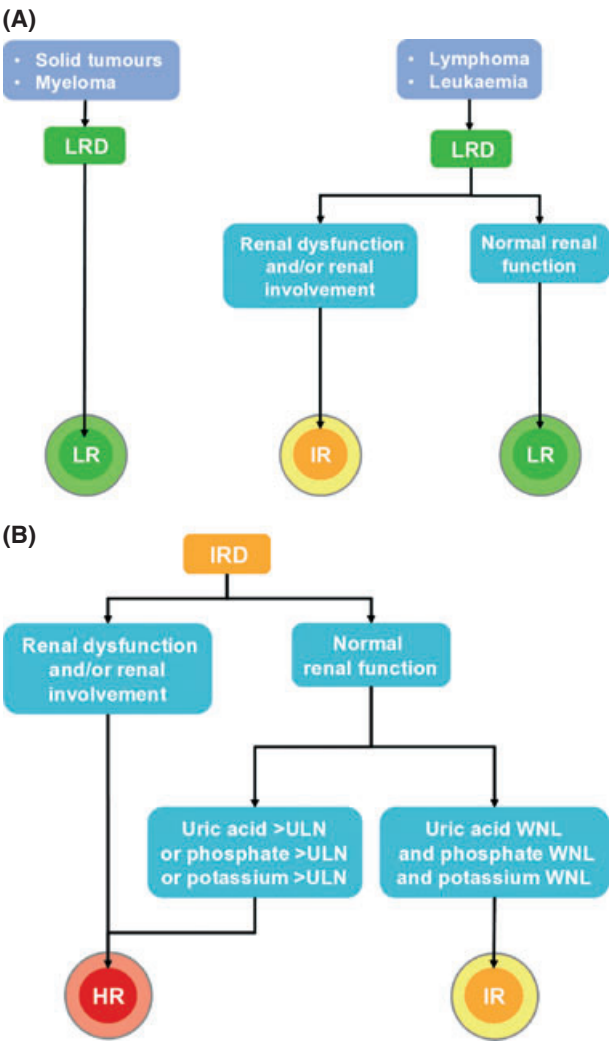

Fig 4. Final TLS risk adjustment is based on renal function. (A) Patients with low risk disease (LRD) are intermediate-risk (IR) for TLS when renal dysfunction and/or renal involvement is present. LR, low risk (B) Patients with intermediate risk disease (IRD) are high-risk (HR) for TLS when renal dysfunction and/or renal involvement is present or uric acid, phosphate or potassium levels are elevated. WNL, within normal limits; ULN, upper limit of normal.

involvement (Fig 4A). Similarly, patients with leukaemias and lymphomas considered to be IRDs were classified as being at a high-risk of developing TLS if there was renal dysfunction and/or renal involvement (Fig 4B). Patients with IRDs and normal renal function would also be high-risk for TLS if their uric acid levels and either phosphate or potassium levels were higher than the upper limit of normal (Fig 4B).

Discussion

The above TLS risk stratification and classification developed by the TLS expert risk panel is a medical decision tree that incorporates histological diagnosis, extent and bulk of disease (stage, LDH, bulk), use of specific cytotoxic agents, age at diagnosis and pre-existing renal dysfunction or renal involvement as major risk factors in this model. The level of evidence (Table I) is based on Harbour and Miller (2001). The risk of developing TLS for patients with LRD was estimated to be <1% with a level of evidence ranging from 2+ to 4 (Table I). The risk of developing TLS for patients with IRD was estimated to be 1–5% with a level of evidence of 1+ to 2+ (Table I). The risk for patients with HRD of developing TLS was estimated to be >5% with a level of evidence of 1++ to 1+ (Table I) (modified Harbour & Miller, 2001).

The prophylaxis recommendations were a modification of the previous review by Coiffier *et al* (2008). The grade of recommendations (Table II) was based on Harbour and Miller (2001). The TLS prophylaxis recommendation based on TLS risk is summarized in Table III. In general, patients with a low risk (LRD) of developing TLS should be monitored for development of TLS and complications; normal hydration and no prophylaxis for hyperuricaemia should be given except in cases of signs of metabolic changes, bulky and/or advanced disease and/or high proliferative disease, in which case

allopurinol should be added (Table III). This grade of recommendation is a level B (Table II). Patients with an intermediate risk (IRD) of developing TLS should be monitored for TLS and complications, administered increased hydration (3l/m^2 per d) and administered allopurinol (100–300 mg, po, q8h, daily) without the need for alkalinization (Table III). This grade of recommendation is a level B (Table II). In patients with high risk (HRD) of developing TLS, frequent monitoring should be performed, increased hydration (3l/m^2 per d), unless evidence of renal insufficiency and oliguria, and rasburicase (0·1–0·2 mg/kg) for one dose and repeated only if clinically necessary. In patients with a prior history of glucose-6-phosphate dehydrogenase, rasburicase is contraindicated and allopurinol should be utilized instead of rasburicase (Table III). This grade of recommendation is a level A (Table II). Furthermore, management of hyperkalemia and/or hyperphosphataemia should be managed as per institutional routine and/or based on previous TLS treatment guidelines (Cairo & Bishop, 2004; Coiffier *et al*, 2008). Lastly, patients who develop LTLS who were originally classified as either LRD or IRD, should receive rasburicase unless clinically contraindicated.

Returning to the two case reports discussed above, in the dialysis patient with DLBCL (Lin *et al*, 2009) the risk classification of this patient would be moved from intermediate to high risk of TLS according to this new risk classification system due to increased LDH levels, renal dysfunction and the presence of bulky disease, while the CLL patient (Vaisban *et al*, 2001) would be elevated from low risk to intermediate risk of TLS due to the presence of pre-existing asotemia. These two examples demonstrate the broad applicability of this new risk classification model and its ability to identify TLS risk even in unusual settings, such as DLBCL, where it is not immediately considered. Importantly, physicians must consider that TLS risk derives from the collective contribution of individual risk factors and is not exclusively associated with a particular malignancy.

This risk classification model, developed by a panel of TLS experts, integrates diverse criteria into a user-friendly, simple

Table III. TLS Prophylaxis recommendations based on TLS risk.

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
ST*	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL†	N/A	N/A
AML and WBC $<25 \times 10^9$/l and LDH $<2 \times$ ULN	AML with WBC 25–100×10^9/l AML and WBC $<25 \times 10^9$/l and LDH $\geq 2 \times$ ULN	AML and WBC $\geq 100 \times 10^9$/l
Adult Intermediate grade NHL and LDH $<2 \times$ ULN	Adult intermediate grade NHL and LDH $\geq 2 \times$ ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH $<2 \times$ ULN	N/A
N/A	ALL and WBC $<100 \times 10^9$/l and LDH $<2 \times$ ULN	ALL and WBC $\geq 100 \times 10^9$/l and/or LDH $\geq 2 \times$ ULN
N/A	BL and LDH $<2 \times$ ULN	BL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	LL stage I/II and LDH $<2 \times$ ULN	LL stage III/IV and/or LDH $\geq 2 \times$ ULN
N/A	N/A	IRD with renal dysfunction and/or renal involvement IRD with uric acid, potassium and/or phosphate >ULN
Prophylaxis recommendations		
Monitoring Hydration ±Allopurinol	Monitoring Hydration Allopurinol	Monitoring Hydration Rasburicase‡

ST, solid tumours; MM, multiple myeloma; CML, chronic myeloid leukaemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphoid leukaemia; AML, acute myeloid leukaemia; WBC, white blood cell count; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALCL, anaplastic large cell lymphoma; N/A, not applicable; ALL, acute lymphoblastic leukaemia; BL, Burkitt lymphoma/leukaemia; LL, lymphoblastic lymphoma.

*Rare solid tumours, such as neuroblastoma, germ cell tumours and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD.

†CLL treated with fludarabine, rituximab and/or those with high WBC ($\geq 50 \times 10^9$/l), should be classified as IRD.

‡Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

and convenient clinical tool designed especially for physicians who frequently see patients at risk for TLS. We recommend that it be adopted and is validated through future international collaborative research efforts.

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Appendix I

TLS Expert Panel

Steering committee: Mitchell S. Cairo (Department of Pediatrics, Medicine and Pathology, Columbia University, New York, NY, USA), Bertrand Coiffier (Department of Haematology, Hospices Civils de Lyon and University Claude Bernard, Lyon, France), Alfred Reiter (Children's University Hospital, Division of Paediatric Haematology and Oncology, Justus-Liebig University, Giessen, Germany) and Anas Younes (The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA).

Participants: André Baruchel (Department of Haematology, Hôpital Saint-Louis, AP-HP, and University Pari Diderot, Paris, France), André Bosly (Department of Haematology, University Hospital of Mont-Godinne, Yvoir, Belgium), Stan C. Goldman (Department of Pediatric Hematology/Oncology, North Texas Hospital for Children at Medical City, Dallas, TX, USA), Guy Leverger (Department of Paediatric Haematology Oncology, Hôpital Armand-Trousseau, AP-HP, Paris, France), Kazuma Ohyashiki (First Department of Internal Medicine, Tokyo Medical College, Tokyo, Japan), Panagiotis Panagiotidis (Aristotle University of Thessaloniki, Thelassoniki, Greece), Andrea Pession (Clinica Pediatrica, Università di Bologna,

Bologna, Italy), Ching-Hon Pui (Department of Oncology, St Jude Children's Research Hospital, and the University of Tennessee Health Science Center, Memphis, TN, USA), Jose-Maria Ribera (Clinical Haematology Department, Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Badalona, Universitat Autònoma de Barcelona, Barcelona, Spain), Giovanni Rosti (Oncology Unit, Ospedale Regionale, Treviso, Italy), Simon Rule (Derriford Hospital, Plymouth Hospitals NHS Trust, Plymouth, UK), Ichiro Tsukimoto (Children's Medical Centre & Institute of Severely Handicapped Children, Saiseikai Yokohamashi Tobu Hospital, Kanagawa, Japan), Pier-Luigi Zinzani (Haematology Unit, Istituto Seragnoli, Ospedale Sant'Orsola Malpighi, Bologna, Italy).